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ADOLESCENT SCHIZOPHRENIA

SMOOTH PURSUIT TRACKING,
VOLUMETRIC MRI, AND WISCONSIN CARD SORTING PERFORMANCE
IN FIRST-BREAK, ADOLESCENT SCHIZOPHRENIA

PH.D THESIS
PRESENTED TO THE SCHOOL OF PSYCHOLOGY
UNIVERSITY OF OTTAWA

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MAY 1998

RUNNING HEAD: ADOLESCENT SCHIZOPHRENIA



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Curriculum Studiorum

Monica Brown, currently working at The Children's Research Centre, Trinity College Dublin. She graduated from a Bachelor of Arts Programme (Honours, Psychology) at the University of Ottawa in 1991, and was awarded a scholarship from the Ontario Mental Health Foundation for her Ph.D. research. She completed her clinical training at the Children's Hospital of Eastern Ontario, and she has specialized skills in the areas of neuropsychology, family/ couples therapy, educational assessment, and programme evaluation,. She has worked in a range of research, teaching and human service settings.

Completed works include the following: *Report of the Research Working Groups' Meeting of the Canadian Alliance for Research in Schizophrenia* (1993, Ottawa); *Towards a more precise definition of sleep onset* (1991, Ottawa); *Mental Health Services in Canada* (1990, Health & Welfare Canada, Ottawa); *Canadian Mental Health Services*, in D. Kemp (Ed.), *The International Handbook of Mental Health Policy* (1994, Connecticut); *Acute Day Hospitalization as an alternative to inpatient treatment*, in the *Canadian Journal of Psychiatry* (1996); *Report of the Workshop for a Multicentre Study of Schizophrenia* (1990, Ottawa). Works in progress include the *Intellectual functioning following surgery for the treatment of intractable temporal lobe seizures in children* (Brown, M., Kuehn, S., & Keene, D.) and an edited version of the Ph.D. thesis.

Presentations include: *Iatrogenic effects on neuropsychological functioning in children treated for Acute Lymphoblastic Leukemia* (1998, Fifth International Conference of the Long-term Complications of Children and Adolescents with Cancer, Niagara-on-the-Lake); *Helping the family cope with Attention Deficit Disorder* (1996, Ottawa); *Don't try to beat them - Join them: How to build partnerships with children* (1997, Ottawa); *Towards a more precise definition of sleep onset* (1991, Ontario University Thesis Conference, Sault-Ste-Marie); *Effective, efficient, and accountable: Using Program Evaluation in the Stroke Service at the Rehabilitation Centre* (1997, Ottawa); *Measuring recovery of communication skills in stroke patients* (1998, Kingston); *Characteristics of sleep onset in pre-adolescents: Temporal relationships among cardiovascular and EEG power spectral measures* (1993, Niagara-on-the-Lake); *Intellectual functioning following surgery for the treatment of intractable temporal lobe seizures* (1997, Dublin).

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Abstract

The purpose of this study was to examine whether impaired smooth pursuit tracking, which has consistently been found in studies of adult schizophrenics, also characterizes adolescents with this disorder. Volumetric brain imaging (MRI) of specific regions thought to be implicated in disordered tracking (i.e., the frontal eye fields and cerebellar vermis), Wisconsin Card Sorting performance (i.e., WCST; a test considered to index frontal lobe functioning), and a measure of the integrity of visual-vestibular interaction were also assessed to examine the possibility of co-occurrence of deficits across patients in order to provide a better understanding of the correlates of impaired smooth pursuit tracking in this disorder. Subjects included 12 adolescents with schizophrenia (6 males, 6 females; mean age = 17.7 years) who were compared to 12 gender- and age-matched normal controls (mean age = 17.1 years). A surprising absence of group differences was found on standard, computer-quantified measures of smooth pursuit tracking (i.e., root mean-square error, gain, and saccades). However, post-hoc analyses using a visual (non-automated) rating scale revealed that the lack of group differences resulted from both controls and patients displaying high rates of impaired tracking. Although analyses of brain volumetrics revealed no overall group differences, two patient sub-groups were identified based on impairments on the WCST and the visual-vestibular index, providing indirect evidence of frontal and cerebellar involvement in these sub-groups, respectively. These results question the usefulness of smooth pursuit tracking impairment in discriminating individuals with schizophrenia from normals at this young age, and are interpreted as providing indirect support for the neurodevelopmental hypothesis of schizophrenia. The need for further studies of smooth pursuit tracking in this population, using a multiparameter approach, is highlighted.

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SMOOTH PURSUIT TRACKING,
VOLUMETRIC MRI, AND WISCONSIN CARD SORTING PERFORMANCE
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INTRODUCTION

A brief overview of schizophrenia

Schizophrenia affects approximately 1% of the general population, with onset typically in adolescence or early adulthood (Thornton & Seeman, 1988). It occurs in both sexes at approximately equivalent rates, although males appear to develop the disorder earlier than females. The course of the illness is, however, thought to be more benign in women. There is a hereditary component in schizophrenia, as the rate of risk increases in proportion to the closeness of the biological relationship to an affected relative. Schizophrenia is heterogeneous in its clinical presentation, characterized by a range of 'positive' (e.g., hallucinations) and 'negative' or 'deficit' (e.g., apathy) symptoms. Acute disturbances of thought processes, perception, mood, and behavior are often present, with residual symptoms evidenced in approximately one-third of patients treated with pharmacotherapy. Neurochemical imbalances (e.g., dopamine) have long been implicated in schizophrenia pathology (Thornton & Seeman, 1988).

Interestingly, over 100 years ago Kraepelin used the term "dementia praecox" to describe what he considered to be a disease of early loss of mental functioning. Less than two decades later, Bleuler used a new name, "schizophrenia", to reflect the clinical presentation of the disorder (i.e., the schism or disconnectedness in ideas, and apparent detachment from reality; Thornton & Seeman, 1988). Only in the last few decades have researchers returned to an

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understanding of schizophrenia as a biologically-based disease, the study of which has been greatly facilitated by technological advances (e.g., in brain imaging). Of particular importance in this regard is the coincidence between the typical period of illness-onset and a number of profound brain changes that occur during the second decade of life, including significant reductions in deep (i.e., stage 4) sleep, cerebral oxygen consumption, and synaptic density (i.e., in the frontal cortex; see Feinberg, 1982, 1987). Maturational reorganization consisting of selective synaptic enhancement and pruning of redundant connections are thought to underly these changes (Feinberg, 1982). A range of other positive findings in schizophrenia (e.g., minor physical anomalies, morphological brain deviations, cytoarchitectural abnormalities) have also recently been interpreted as supporting the hypothesis that schizophrenia is a disease of *neurodevelopment* rather than of *neurodegeneration* (Weinberger, 1995).

The search for biological markers of schizophrenia has been impeded by its heterogeneity, a factor that is thought to contribute to the inconsistent and highly variable results observed (Lieberman, Jody, Alvir, & Ashtari, 1993). However, one robust finding has been that of impaired smooth pursuit eye tracking performance, the pathophysiologic significance of which is not yet known. Tracking deficits have been the focus of a great number of investigations, but only recently have they been studied in combination with other procedures (e.g. brain imaging or neuropsychological testing). No specific examination has been made of brain areas thought to be involved in smooth pursuit tracking (i.e., the frontal eye fields, cerebellum). Furthermore, there have been no reports focussed exclusively on identifying whether, and to what degree, this impairment is present in those patients with adolescent-onset schizophrenia. Previous studies have clearly included at least one adolescent, as indicated by the age ranges reported (e.g.,

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Iacono, Moreau, Beiser, Fleming, & Lin, 1992; Lieberman et al., 1993), but no special attention has been given to the analysis or presentation of data from this young group of patients.

Rationale for the current investigation

The importance of considering schizophrenia within a developmental context has long been recognized. Research aimed at assessing the behavioral and neurobiological aspects of individuals at risk for developing schizophrenia has revealed the presence of early signs and dysfunctions which are potential vulnerability markers for this disorder (e.g., see Erlenmeyer-Kimling & Cornblatt, 1987; Fish, 1987; Marcus, Sydney, Auerbach, Mirsky, & Aubrey, 1987). Studies of childhood-onset schizophrenia (i.e., typically diagnosed before age 10) have suggested similar patterns of clinical presentation and deficits to those of adults with the disease, with the one difference being a more severe course and poorer prognosis ascribed to the former group (Asarow, Tompson, & Goldstein, 1994). Little research has been conducted specifically with individuals who experience illness-onset in adolescence, but it is thought that this group can be distinguished from the adult-onset group in that they also tend to show a poorer clinical outcome (Gillberg, Hellgren & Gillberg, 1993).

The majority of schizophrenia research has focussed on identifying psychophysiological, brain, and cognitive deviations or impairments in adult patients with chronic schizophrenia. The results of these studies have provided strong evidence in support of impaired smooth pursuit tracking, structural brain deviations (e.g., global and regional), and poor performance on neuropsychological tasks purported to assess frontal-lobe functioning. Only recently has the focus of research shifted to studies of younger patients to establish whether these specific

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deviations are also present at illness-onset, as a first step in assessing whether or not they may be considered early markers of the disease. It is expected that differences identified early in the disease process may contribute to a greater understanding of disease etiology and variability (i.e., course and symptomatic presentation), and may facilitate diagnosis and sub-typing. To date, however, studies of first-break patients still include a heterogeneous group with respect to the age of diagnosis/ symptom-onset (i.e., from late adolescence to adults in their twenties), and the data on the adolescent sub-group have not been presented separately, indicating a lack of recognition of the potential distinctiveness of this sub-group (e.g., in terms of frequency or severity of observed deficits and the potential impact of developmental factors on these deficits). The specific correspondence of the period of adolescence with the typical illness onset period in schizophrenia (Findling, Friedman, Kenny, Swales, Cola, & Schulz, 1995), and the developmental changes associated with adolescence generally, strongly argue for this group to be the specific focus of investigation.

The present study therefore was formulated in response to the need for data to be collected during what is thought to be a critical developmental period for schizophrenia, i.e., adolescence. The selection of dependent measures for the current investigation, i.e., smooth pursuit tracking, volumetric brain measurements of the frontal eye fields and cerebellar vermis, and performance on the Wisconsin Card Sorting Test (WCST), was guided by the results of previous studies of adult, chronic schizophrenic patients showing strong evidence of impaired tracking and a variety of brain abnormalities. Impaired smooth pursuit tracking, perhaps the most robust finding in the adult schizophrenia psychophysiological literature to date, has rarely been examined in adolescent patients. Furthermore, the specific brain regions thought to be implicated in

disordered tracking have not been quantified (i.e., through volumetric analysis) in any patient or control groups. Information is also lacking with respect to the performance of adolescents on the most widely-used neuropsychological task in schizophrenia research, i.e., the WCST. A multiparameter approach was employed in the present investigation to facilitate understanding of the extent to which these impairments are present at illness-onset in schizophrenia.

Disordered eye movements in schizophrenia

Characterizing the tracking deficit

Two distinct but interacting oculomotor systems work together to effect visual fixation. The *smooth pursuit* system, which normally requires the presence of a visible, moving target for activation, works to continually match eye to target velocity to maintain a stable image on the retina (Robinson, 1965; Pivik, 1979). The *saccadic* system utilizes high velocity eye movements to bring the image of a target onto the fovea (e.g., in scanning the stationary environment), and, during tracking of a moving object, this system also corrects for position error if the eye begins to lag behind the target (Iacono, Tuason, & Johnson, 1981). Although the saccadic system functions somewhat automatically in response to routine information processing demands, saccadic movements are under a degree of voluntary control (Iacono et al., 1981). Movement of 20° amplitude or less is normally completed with a single saccade, and latency is somewhat slower than for other psychomotor responses because the final eye position must be determined before the response is executed (Carpenter, 1977).

Unimpaired smooth-pursuit tracking of pendular motion is reflected in the electrographic record as a smooth sine wave as the eye mirrors the changing pendulum velocity, although

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occasional inattention and pursuit movement discontinuity are normal (Holzman, Proctor, & Hughes, 1973). The observed tracking deviance in schizophrenic patients often appears as if a number of fast, horizontal saccadic movements have been superimposed on the pursuit movement (Holzman et al., 1973). Although visual rating scales have been used to index the level of deviant tracking in schizophrenia (Benitez, 1970; Shagass, Amadeo, & Overton, 1974), performance on the pendulum task has also been more objectively quantified. A phase-corrected *root mean square* (RMS) error measurement commonly has been used to provide a general indication of the extent to which tracking and target patterns can be superimposed (Iacono & Lykken, 1979). The *pursuit gain* index allows comparison of eye tracking and target displacements by expressing the relationship of smooth eye velocity to target velocity as a ratio (Van Den Berg & Collewyn, 1986). Two other commonly used scores include the *positive saccades* (PS) score (the total number of times eye velocity exceeds maximum target speed by $33^{1/3}$ %), and the *velocity arrest* (VA) score (a count of the number of times the eye slows significantly, with pursuit velocity $< 2^\circ/\text{sec}$, ≥ 40 msec duration; Holzman et al., 1973; Shagass et al., 1974; Pivik, 1979). Other indices of tracking performance have been used, including *signal-to-noise ratio* (i.e., a global measure), *corrective catch-up saccade rate and amplitude*, *square-wave jerk rate*, *number of anticipatory saccades*, and *total time engaged in smooth pursuit* (Friedman et al., 1995a).

Disordered smooth pursuit eye movement has been found in individuals with schizophrenia and other psychotic disorders. Diefendorf and Dodge (1908) first observed aberrant tracking of pendular motion among patients with dementia praecox, and more recent investigations have confirmed these early findings (Holzman et al., 1973, 1974a; Shagass et al., 1974; May, 1979;

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Cegalis & Sweeney, 1979; Pivik, 1979; Iacono et al., 1981; Bartfai, Levander, Nyback, Berggren, & Schalling, 1985; Spohn, Coyne & Spray, 1988; Tien, Ross, Pearlson, & Strauss, 1996). A comprehensive review of the literature conducted by Levy and associates (1993) found more than 80 replications of the smooth pursuit dysfunction finding in schizophrenic patients. The observed impairment, typically assessed in terms of total spatial discrepancy between smooth pursuit tracking response and target position (i.e., root mean square error), saccadic intrusions, and/or low-gain pursuit, has been found in 50 to 80% of patients studied. The proportion of younger, first-episode patients who show disordered tracking remains unclear, as both similar (i.e., Lieberman et al., 1993), and lower rates (i.e., 20%, Iacono et al., 1992) have been reported.

There is a lack of information regarding the prevalence of the observed deficit in psychotic and/or schizophrenic adolescents. Results from a recent study of a group of 17 young adolescents (mean age 14 years), diagnosed on average 4 years earlier with childhood schizophrenia, and unresponsive to traditional neuroleptic treatment, showed impaired tracking relative to controls (Gordon et al., 1994; Jacobsen et al., 1996). Unfortunately, the majority of these individuals were receiving clozapine, a newly re-introduced drug which is known to impair tracking performance (Gordon et al., 1994). Data on the quality of eye tracking performance in young normal controls is also lacking, although there is evidence of significant improvements with age when comparing the performance of pre-adolescents (i.e., 11-12 years) and those in late adolescence or adulthood (Katsanis, Iacono, & Harris, 1998; Accardo, Pensiero, DaPazza & Perissutti, 1995; Ross, Radant, & Hommer, 1993), suggesting the need for attention to be given

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to the developmental issues in eye tracking, and perhaps to other deficits associated with schizophrenia.

Disordered smooth pursuit tracking is not specific to schizophrenic syndromes. Deviant tracking has also been found in patients with affective psychoses (Shagass et al., 1974; Shagass, Roemer & Amadeo, 1976; Muir, St.Clair, Blackwood, Roxburgh, & Marshall, 1992), general paresis (Diefendorf & Dodge, 1908), encephalitis, multiple sclerosis, Parkinson's disease, various brainstem lesions, and barbiturate intoxication (Jung & Kornhuber, 1964). It has also been found fairly consistently, but to a lesser extent, among patients with bipolar illness (23 to 41%; Holzman et al., 1973, 1974a; Holzman, Solomon, Levin, & Waternaux, 1984; Iacono et al., 1992) -- a result which may be more related to lithium carbonate treatment than underlying pathology (Levy et al., 1985). It has also been suggested that eye movement abnormalities in neurologic and affective disorders, unlike those observed in schizophrenia, may be a function of clinical status (Bartfai, Wirsén, Levander, & Schalling, 1989) rather than reflecting a more stable phenomenon, displayed by schizophrenic patients in remission as well as those who are acutely ill (Spohn et al., 1988). Less than 10% of normal controls show disordered tracking (e.g., Holzman et al., 1973, 1974a; Iacono et al., 1992).

The observed tracking deficits in adults do not seem to be attributable to the confounding effects of age or gender (Shagass et al., 1974; Holzman et al., 1974b; Kuechenmeister, Linton, Mueller, & White, 1977; Pivik, 1979). Although the potential confounding influence of neuroleptic medication can not be dismissed (Troost, Daroff, & Dell'Osso, 1974), no significant drug effects on tracking performance have been reported (Bartfai et al., 1985; Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975; Holzman et al., 1973; Shagass et al., 1974; Jones &

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Pivik, 1983; 1985). Poor tracking has been identified in chronic schizophrenic patients prior to and following a 10-day wash-out period (Holzman et al., 1974b), and in drug-naïve patients (Campion et al., 1992). The long-term effects of neuroleptics on eye-tracking have not been sufficiently studied, and this potential confound cannot easily be dismissed since chronic patients are commonly used as subjects in these studies. However, it has been suggested that medication may improve tracking in patients (Holzman et al., 1974b), and its withdrawal may worsen performance (Spohn et al., 1988). Clearly, studies using never-, non-, or recently-medicated subjects might allow clarification of the relationship between medication and disordered tracking in psychosis.

Eye tracking dysfunction has been considered a biological marker for schizophrenia (Clementz & Sweeney, 1990; Szymanski, Kane & Lieberman, 1991), and has been proposed as a genetic marker to study the transmission of vulnerability to schizophrenia (Holzman et al., 1974a). A significantly higher proportion of first degree relatives of schizophrenic patients show deviant tracking, compared with relatives of nonschizophrenic patients (e.g., 44% vs 10.5%, Holzman et al., 1974a). Such a relationship has not been found for tracking deficits among manic-depressive patients and their family members (Iacono, Peloquin, Lumry, Valentine, & Tuason, 1982). Greater concordance for tracking impairments among monozygotic versus dizygotic twins discordant for schizophrenia has also been reported (Iacono & Lykken, 1979; Holzman, Kringlen, Levy, & Haberman, 1980). Generally, the results of more than two decades of research suggest that the tracking deficit is a meaningful finding which may be helpful in understanding schizophrenia.

The meaning of eye movement dysfunction

Attentional deficits have been postulated to account for a range of findings in schizophrenia (see reviews by Braff, Swerdlow, & Geyer, 1995; Oades, 1995; Hemsley, 1996), and they continue to be regarded as one of the possible dysfunctions underlying poor tracking. Holzman and colleagues (1973) concluded that "superficial" inattention did not account for deviant tracking demonstrated by schizophrenic subjects, although the presence of a "core" attentional deficit was not ruled out. Subjects have shown little (Brezinova & Kendell, 1977) or no (Shagass et al., 1974; Holzman et al., 1974a) improvement in tracking performance as a result of realerting instructions. Psychotic patients (Holzman et al., 1974a) and psychiatric inpatients (Pivik, 1979) have been shown to make more tracking errors even following realerting. More continuous, attention-engaging stimuli (e.g., tracking while silently reading a changing numerical stimulus) have been shown to improve tracking over baseline (i.e., standard stimulus tracking) performance, although significant tracking differences between patients and controls are maintained (Shagass et al., 1976).

Of interest is the observation that the addition of an attention-monitoring task (e.g., button-press response to unsignalled target interruption) can negatively affect tracking in psychiatric inpatients (Pivik, 1979). Acute sensitivity to distraction or information-processing overload, which are prominent among explanations of reduced attention among psychiatric patients (especially schizophrenia), may be significant factors underlying the observed tracking deficits (Pivik, 1979). This underlying dysfunction may also be conceptualized in terms of effort or working capacity, as poor tracking similar to that observed in schizophrenia can be induced by the addition of a serial subtraction task during tracking (Brezinova & Kendell, 1977). Realerting

has also been shown to increase blinking rates in psychiatric inpatients and outpatients, while decreasing it in controls (Pivik, 1979), findings which may be interpreted as evidence that this procedure is somewhat stressful. Chronic schizophrenics show higher blinking rates and more interrupted tracking compared to acute patients, and it has been proposed that these chronic patients must expend considerable effort in order to track a pendulum -- effort which cannot be sustained for the duration of the task (Cegalis & Sweeney, 1976). Patients also have more difficulty than controls getting on-task (i.e., the degree of initial engagement of attention is less; May, 1979). Clearly, although a portion of performance error may be the result of voluntary inattention or lack of motivation (Shagass et al., 1976; Holzman, Levy, & Proctor, 1978), there is a residual deficit between psychiatric patients' and controls' tracking that remains to be explained (Pivik, 1979).

In contrast to their smooth pursuit tracking performance, normal saccadic eye movements have been found among actively-ill schizophrenic (Diefendorf & Dodge, 1908; Levin, Jones, Stark, Merrin, & Holzman, 1982) and manic-depressive patients (Levin, Lipton & Holzman, 1981), and bipolar and unipolar affective disorder patients (Iacono et al., 1982). These findings have been interpreted as evidence that saccadic movements during smooth pursuit tracking may reflect a requirement for multiple corrections in response to numerous tracking errors or increase in phase lag (Iacono & Koenig, 1983), or alternately, may reflect disinhibition of the saccadic system itself. These hypotheses are consistent with interpretations involving disturbances of nonvoluntary attention in psychoses (Levin et al., 1982). Because eye tracking performance can be improved under certain conditions, it seems unlikely that muscular or retinal pathology underlies the observed deficit (Shagass et al., 1976; Iacono et al., 1981; Levin, 1984), although

this remains a possibility (Meltzer & Crayton, 1974; Stevens, 1974). It is generally agreed that cortical control of these two types of eye movements are separate (Bach-y-Rita, 1971) and disordered pursuit (and the associated lack of saccadic disturbance) has therefore often been attributed to a cortical disturbance (Iacono et al., 1981; Levin, 1984).

Cortical and subcortical contributions to eye movement dysfunction

Although the basis of deviant smooth pursuit tracking in schizophrenia has not been determined, there are data to support both cortical and subcortical contributions to this dysfunction. In particular, frontal and cerebellar structures are thought to influence smooth pursuit eye movements, and deviant tracking (e.g., saccadic tracking of slow-moving targets) has been considered to be a sensitive index of central nervous system pathology.

Cortical contributions

Cortical contributions to the eye tracking dysfunction in schizophrenia have been emphasized. In particular, the frontal eye field (area 8) and dorsomedial cortex are known to control voluntary saccades (Robinson & Fuchs, 1969), encoding the goal of the eventual saccade (Dassonville, Schlag, & Schlag-Rey, 1992), and project to the superior colliculus, which is involved in reflexive eye movements (Illing & Graybiel, 1985). Other major sources of interaction with the frontal eye fields include the basal ganglia, the cerebellum (i.e., the posterior vermis and flocculus), and the reticular formation (Stanton, Goldberg, & Bruce, 1987). The cells of the frontal eye fields have been shown to fire selectively during smooth pursuit movement and are thought to regulate inhibitory mechanisms involved in saccadic movement

control (Bizzi, 1968). Clearly, the region of the frontal eye fields and/or associated pathways are candidates for involvement in schizophrenia.

Despite strong evidence implicating the frontal eye field region in smooth pursuit control, there are as yet no published imaging studies examining volumetric or functional changes in this specific brain area in schizophrenia. At the time the current study was developed, there were only two published studies examining both tracking performance and brain imaging (i.e., of global structural cortical abnormalities) in the same sample of patients. These studies were based on global measures and showed no clear association between tracking performance and structural brain abnormalities (Bartfai et al., 1985; Smeraldi et al., 1987). Lieberman and colleagues (1993) examined a variety of brain regions and reported that approximately one-third of first-episode schizophrenic patients (aged 16 to 40 years, mean of 24 years) showed evidence of regional and/or global brain pathology (i.e., on a 3-point qualitative visual rating scale), with some of those patients also showing disordered tracking and/or increased central nervous system dopamine responsivity. Multiparameter studies involving brain imaging are relatively rare in schizophrenia research in general, but would appear to be crucial to advancing the understanding of smooth pursuit tracking impairments.

Although the specific hypothesis that differences in the frontal eye fields may exist (and may be related to smooth pursuit tracking impairments) has not been directly assessed, there is strong evidence to support the general hypothesis of frontal lobe involvement in schizophrenia. The frontal lobes have been implicated in aspects of schizophrenia symptomatology (e.g., attention, information processing, and avolition; Levin, 1984; Fukushima et al., 1988, 1990, 1994) -- symptoms which are commonly seen in association with frontal lobe injury and dementia

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(Kertesz, Davidson, & Fox, 1997). Poorer performance by schizophrenics on tasks thought to be subserved by the frontal lobes has also been a common finding. Specifically, poorer performance on the WCST, which has served as a useful index of frontal lobe functioning (Milner, 1963; Drewe, 1974), has been interpreted as evidence of frontal neuropsychological deficits in adult (Fey, 1951; Heaton, Baade, & Johnson, 1978; Kolb & Whishaw, 1983; Weinberger, Berman, & Zec, 1986; Goldberg, Weinberger, Berman, Pliskin & Podd, 1987; Goldberg, Berman, Mohr, & Weinberger, 1990) and adolescent schizophrenia (Kenny et al., 1997), and in those at risk for schizophrenia (i.e., schizotypic, Lenzenweger & Korfine, 1994). This simple neuropsychological test has also been used extensively in functional imaging studies as an activation test of the frontal lobes in schizophrenia. A recent review of these functional imaging studies has, in fact, revealed *hypofrontal* activation as the most consistent finding to date (i.e., as measured during 'resting' states and during activation typically using the WCST), with preliminary support for the hypothesis of a fronto-striatal dysfunction in schizophrenia (Velakoulis & Pantelis, 1996). Similar results have been found in newly diagnosed patients with schizophrenia and schizophreniform disorder (Rubin et al., 1994), and in a small group of adolescents with initial-stage schizophrenia (Batista et al., 1995). Resting *hyperfrontality* in neuroleptic-naïve, acute schizophrenic patients has also been found in a single positron emission tomography (PET) study of glucose metabolism, suggesting the possibility of frontal *hyperinnervation* (Szechtman, Nahmias, & Garnett, 1988).

Recent research endeavours have also provided some evidence to indicate volumetric changes in the frontal lobes in schizophrenia. Smaller global frontal volumes have been found in chronic schizophrenics (Woods, Yurgelun-Todd, Goldstein, Seidman, & Tsuang, 1996) and in

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patients at illness-onset (Lieberman et al., 1993; Napoulous et al., 1995), compared with normal controls. Andreasen and colleagues (1986) found that approximately 40% of schizophrenics in their study had smaller frontal lobes and cranial size than controls, but this result was not replicated in a similar study conducted by these researchers 4 years later. A lack of differences on global volumetric measurements of the frontal lobes between children with symptoms of schizophrenia and normal controls has also been reported (Hendren et al., 1995). Only one published study has assessed differences in a specific frontal lobe region. Seidman and colleagues (1994) reported on the association between poor performance on the WCST and smaller dorsolateral prefrontal cortical areas in chronic schizophrenic patients. Overall, given the results of these few studies, it is clear that some degree of frontal lobe involvement would be expected in at least a portion of individuals with this disease, both at illness-onset and later in the course of the disease.

The study of specific brain regions such as the frontal lobes is a relatively recent occurrence in the imaging research in schizophrenia. The majority of structural brain imaging research conducted to date has focussed on comparing schizophrenic patients and normal controls on global features of brain dysmorphology (see the extensive review by Pfefferbaum & Marsh, 1995). From this research, there is overwhelming evidence of global brain involvement in this disorder. A large proportion of chronic schizophrenics (i.e., typically between 20 to 40%) have shown evidence of sulcul dilation and/or enlarged ventricles (Weinberger, Cannon-Spoor, Potkin, & Wyatt, 1980; Weinberger, Wagner, & Wyatt, 1983; Lawson, Waldman, & Weinberger, 1988; McCarley et al., & Duffy, 1989; Pearlson et al., 1989; Rossi, Stratta, Gallucci, Passariello, & Casacchia, 1989; Stratta et al., 1989; Andreasen et al., 1990b; Zipursky, Lim, Sullivan, Brown,

& Pfefferbaum, 1992). Ventricular enlargement has also been found in both adolescent (Schulz et al., 1983) and older first-episode patients (Nyback, Weisel, Berggren, & Hindmarsh, 1982; Lawson et al., 1988; Iacono et al., 1988; DeLisi et al., 1991; Degreef et al., 1992; Lieberman et al., 1993)¹. These structural abnormalities have been found to be correlated with impaired performance on neuropsychological tests, poor premorbid adjustment, poor response to drug treatment, and the presence of negative symptoms (Crow, 1980; Andreasen, Olsen, Dennert & Smith, 1982), but uncorrelated with length of illness, amount of pharmacological treatment (Shelton & Weinberger, 1986), ongoing level of psychopathology (Lawson et al., 1988), and electro-convulsive treatment (Roberts, 1983)².

In summary, there is a striking lack of research combining both smooth pursuit tracking assessment and brain imaging, specifically of the frontal eye fields, in schizophrenia. There is strong support for the hypothesis of frontal lobe involvement in schizophrenia in general, arising mainly from the results of functional imaging and poor performance on the WCST. Some evidence of volumetric differences in the frontal lobes has also emerged in recent years, and there is a wealth of evidence to suggest that global brain changes characterize a sub-group of individuals with schizophrenia, both at illness-onset and later in life.

Subcortical Contributions

Cortical dysfunction has been emphasized as an important consideration in understanding the observed smooth pursuit impairment, but the contribution of subcortical structures also needs to be examined. One subcortical system which may contribute to the observed eye-tracking disorder in schizophrenia is the vestibular system. This system plays a critical role in normal postural and visual-motor behavior, and dysfunction of this system has been implicated in

sensory information processing and integration impairments associated with psychotic symptomatology (Ornitz, 1970; King, 1974). Generally, research findings attest to the integrity of the vestibular system in psychotic patients (Jones & Pivik, 1983; Levy, Holzman & Proctor, 1978; Lipton, Levin & Holzman, 1980), although disturbances of the interaction between the visual and vestibular systems have been demonstrated (Jones & Pivik, 1983; 1985; Cooper, 1987; Cooper & Pivik, 1991).

One of the indices that has been used to assess the integrity of visual-vestibular interaction in the vestibulo-ocular reflex (VOR). The VOR generates compensatory eye movements in response to head movement to stabilize fixation on stationary targets and maintain perceptual constancy, and the VOR system must be suppressed during pursuit of moving targets to allow fixation (Chambers & Gresty, 1983)³. With inadequate fixation suppression, the VOR continuously moves the eyes off the target, such that repetitive saccades are required to refixate the target (Zee, 1977). Fixation suppression abnormalities have been found in patients with posterior fossa lesions (Alpert, 1974), and cerebellar atrophy (Baloh, Jenkins, Hornrubia, Yee, & Lau, 1979), and these abnormalities have been correlated with smooth pursuit dysfunction (Zee, 1977; Chambers & Gresty, 1983; Jones & Pivik, 1985).

Vestibular activation can be achieved through caloric irrigation, and subsequent fixation and tracking procedures can assess visual-vestibular interaction. Jones and Pivik (1985) found that actively psychotic patients showed a significant failure of visual fixation suppression which was related to a higher incidence of tracking errors during baseline and post-irrigation conditions -- a relationship not evidenced in normal controls or a comparison group of schizophrenic outpatients with remitted symptomatology. Reduced fast phase (saccadic) velocity and dysrhythmic

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nystagmus were also observed in the same patients. It was suggested that a disorder of VOR modulation, rather than structural damage to this system, was responsible for the observed deficits. Furthermore, these findings were suggestive of dysfunctioning of brain stem mechanisms, while not excluding a cerebral contribution to VOR suppression (Takemori, Ono, Maeda, 1979) and pursuit tracking deficits (Jones & Pivik, 1985).

Some investigators have emphasized the role of cerebellar and brainstem structures in smooth pursuit tracking and the suppression of caloric nystagmus by ocular fixation (Alpert, 1974; Baloh et al., 1979; Baloh, Yee, Kimm, & Hornrubia, 1981; Kato et al., 1979; Kato, Nakamura, Koike, & Watanabe, 1982; Ito, Nisimaru, & Yamamoto, 1973)⁴, particularly the posterior vermis of the cerebellum (Stanton, Goldberg, & Bruce, 1987; Vahedi, Rivard, Amarenco, & Pierrot-Deseilligny, 1995). Of interest in this regard is the observation that the smooth pursuit tracking in psychotic patients improves considerably under dark conditions (as compared to standard light testing conditions), such that their performance is no longer significantly different from normals' (Pivik, Bylsma, & Cooper, 1988). Cerebellar influence on eye movements is greatly reduced under dark conditions (Hood & Waniowski, 1984). Therefore, these results have been interpreted as evidence for cerebellar dysfunction, resulting in the disinhibition of eye movements during fixation. Cerebellar dysfunction could also contribute to the observed tracking deficit among these patients in the form of excessive saccadic intrusions during tracking which involuntarily directs attention away from the target.

Indirect support for cerebellar involvement is provided by previous reports of suspected cerebellar atrophy in schizophrenic patients (Weinberger, Torrey, & Wyatt, 1979; Weinberger, Kleinman, Luchins, Bigelow, & Wyatt, 1980; Dewan et al., 1983). Results have been mixed

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with respect to findings of fourth ventricle enlargement (Alyward et al., 1994; Yates, Jacoby, & Andreasen, 1987; Nasrallah, Schwarzkopf, Olson, & Coffman, 1991), which has been considered an indirect sign of reduced vermal tissue volume (Dewan et al., 1983). Cerebellar damage is thought to result in hippocampal overactivity and septal underactivity which may lead, respectively, to the symptoms of emotional disturbance and anhedonia observed among schizophrenic patients (Roberts, 1983). The integrity of cerebellar-thalamic-prefrontal circuitry has also been implicated in motor-cognitive tasks involving rapid coordination of activities (Andreasen et al., 1996).

Synopsis and hypotheses

Schizophrenia has been studied using a range of paradigms and techniques. However, attempts to synthesize this wealth of research into an integrated understanding of the disorder have been frustrated by a general lack of information regarding the co-occurrence of abnormal results within a given diagnostic category and within a given patient (Iacono, 1985; Seidman, 1983). Clearly, the use of multiple investigative techniques can provide individual neurodiagnostic profiles and a more accurate estimate of the frequency of observed abnormalities (Seidman, 1983). Furthermore, sub-groupings based on the observed abnormalities may also enhance the understanding of disease presentation, prognosis, and treatment. With the potential that the multiparameter approach holds, it is surprising that smooth pursuit impairment, one of the most robust findings in the schizophrenia research to date, has rarely been examined alongside the assessment of brain abnormalities or neuropsychological functioning.

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In light of these considerations, the present study used a multiparameter approach to study groups of schizophrenic and normal adolescents. Smooth pursuit tracking performance was assessed under dark and illuminated conditions and during vestibular activation. Volumetric brain imaging of areas thought to be implicated in the tracking impairment, but which have not yet been the focus of study, were also examined (i.e., frontal eye fields, cerebellar vermis). Performance on the WCST was also assessed. As only a few studies have examined WCST performance in adolescent schizophrenia, this measure was included in the present investigation to attempt to replicate the finding of impairment in this young group. It was also included as an putative index of frontal lobe functional integrity. Assessment of the integrity of the interaction between the visual and vestibular systems (i.e., reflected by the degree of fixation suppression following caloric irrigation) was included as an index of posterior cerebellar vermal function. The examination of smooth pursuit tracking under dark conditions also provided a means of understanding whether the cerebellum might be implicated in this sample.

The present study addressed the following three main issues: (1) Are smooth pursuit eye movement tracking deficits, considered putative biological markers of psychosis in adults, present in adolescents at the time of their first psychotic episode?; (2) Are volumetric differences present in the areas of the frontal eye fields and the cerebellar vermis (particularly the posterior vermis) at this time?; and, (3) Is performance on a neuropsychological measure thought to reflect the integrity of frontal lobe functioning impaired in this sample of young schizophrenics? These questions were examined using both group comparisons (i.e., first psychotic episode adolescents versus control subjects) and, where appropriate, case-by-case analyses.

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Based on the preceding review of the literature, which showed convincing evidence of smooth pursuit tracking deficits, brain involvement of some kind in at least a large proportion of individuals with schizophrenia, and poor performance on the WCST, the following specific hypotheses were proposed:

Relative to normal controls, adolescents close to the onset of their first psychotic break will show:

- 1) poorer smooth pursuit tracking performance (i.e., as indicated by higher root-mean square tracking error; lower gain; higher saccade scores) and reduced suppression of vestibular nystagmus by visual fixation following caloric irrigation. Improvements in smooth pursuit tracking across conditions (i.e., dark improvement relative to illuminated and vestibular activated) are anticipated, with the relative magnitude of the improvement expected to be larger for the patient group.
- 2) smaller volume measures in the frontal eye fields and/or cerebellar vermis regions, and enlargement in the fourth ventricle (i.e., an indicator of cerebellar tissue reduction; Dewan et al., 1983).
- 3) poorer performance on the WCST compared to normal controls.

A series of post-hoc exploratory analyses will be conducted to examine the co-occurrence of abnormalities in patients. Intercorrelations between the indices (i.e., tracking, brain imaging, WCST) will be explored using multivariate regression analyses and a series of bivariate correlational analyses. As the literature review yielded little or no information regarding whether gender differences could be expected on any of the dependent measures, no specific a priori hypotheses were made in this regard, but exploratory, post-hoc analyses will be conducted.

METHODOLOGY

Subjects

Patients were recruited from local hospital Departments of Psychiatry. Diagnosis and presence of psychotic symptomatology were assessed by one of three psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition -- Revised (DSM-III-R; American Psychiatric Association, 1987) and Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1977). Because the diagnosis of schizophrenia requires that the identifying symptomatology be present for at least 6 months, a provisional diagnosis of schizophreniform disorder is usually made in the case where schizophrenia is suspected. For the present investigation, definitive diagnoses were made at the time of a 6-month follow-up assessment with the psychiatrist. Control subjects were recruited from the local population on a volunteer basis through poster advertisement.

For inclusion in the study, all subjects were screened for: a minimum IQ score of 80 on the Wechsler Adult Intelligence Scale -- Revised (WAIS-R) or the Wechsler Intelligence Scale for Children -- Revised (WISC-R); an intact right tympanic membrane; and an unobstructed external auditory canal as determined by otoscopic examination. Subjects were also excluded if they reported a significant neurological history, past or current substance abuse, or conditions considered as contraindications for MRI use (e.g., presence of metallic foreign bodies in the head, face, neck),

Fifteen patients were screened for inclusion in the study. Of these, one was excluded due to a low score on intelligence testing, and two others were excluded because of anxiety regarding

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the testing procedures. On average, the twelve remaining patients underwent testing procedures within 4.3 months of the date of their first admission to hospital (range 2 to 9 months).

Twelve normal controls were selected from a pool of subjects to match the patients on the dimensions of gender and age [6 males, 6 females in each group; age [$\bar{x}$ (SD): patient = 17.73 (1.58) years, range 14-20 years; control=17.05 (1.08) years, range 14-19 years]. Controls were excluded on the basis of familial history of mental illness or personal history of organic disease or head injury, ongoing medication or drug use (e.g., antihistamines, tranquillizers, barbituates, alcohol), or abnormal response profiles on the Minnesota Multiphasic Personality Inventory. All subjects reported at least average academic progress to date, with all patients experiencing a recent disruption in their normal educational program as a result of the recent decline in their psychiatric status and hospitalization. All subjects reported right-hand dominance.

Experimental procedures were explained to all prospective subjects before obtaining written informed consent from the subject and/or parent. Subjects were then assigned a code number randomly selected by a research assistant to ensure that data analyses could be conducted without reference to subjects' names, group membership, or clinical status. This code was broken following scoring of electronic, neuropsychological, and imaging data to allow statistical analyses and interpretation of results.

Procedure

Clinician Ratings

For all subjects, adolescent sexual maturation stage was assessed by a psychiatrist using a rating scale developed by Tanner (1966). These ratings were made to control for potential group differences in developmental stage.

The Brief Psychiatric Rating Scale (BPRS; Overall & Gorman, 1962), Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay, Fiszbein & Opler, 1987), and the Global Assessment Scale (GAS; Endicott, Spitzer, & Fleiss, 1976) were completed by the treating psychiatrist at the time of the adolescent's first psychotic episode. These ratings served as indices of the presence and severity of clinical symptomatology in the patient group.

Eye movement recordings

Smooth pursuit eye movements

Subjects were assessed individually. Beckman miniature silver-silver chloride electrodes were attached to the outer canthus of each eye for recording the horizontal electrooculogram. Vertical eye movements and blink artifact were monitored from similar electrodes placed above and below the right eye. Eye movements were recorded on direct coupled amplifiers with broad frequency response characteristics (DC - 300Hz). A ground electrode was placed in the mid-forehead area. Electrodes were also attached for recording of electroencephalographic (EEG: O2/A2) and facial electromyographic (EMG; orbicularis oris) activities. Subjects were informed that the polygraphic records would allow remote monitoring of their level of arousal in an attempt to increase their motivation to remain alert and to maintain attention to the task. Facial

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muscle tension and movement artifact were obtained from EMG recordings. Electrographic and stimulus-response data were recorded on polygraphic paper writeout and magnetic tape. All testing procedures were controlled through a microprocessor.

During electrographic recordings, subjects reclined on a cot with their heads slightly elevated and stabilized by supports to reduce head movement. A computer-controlled panel containing a series of light emitting diodes (LEDs; 2 mm diameter each) was positioned at eye level 1 meter from the subjects. The task required subjects to visually track the apparent motion of a single, moving dot of light, oscillating at a rate of 1 excursion every 2.2 seconds (.45 Hz; maximum visual angle of $\pm 10^\circ$ from center). Subjects were instructed to track the target as closely as possible, and to press a hand-held button when the target light was interrupted (off-cycle, 200 msec; 6 interruptions randomly distributed in each condition starting after the 2nd oscillation), in order to assess the potential confounding effects of voluntary inattention on task performance. Seven practice oscillations were provided to ensure subjects were tracking and responding as requested.

Subjects completed the tracking task under 3 conditions: in the presence of ambient light; in the dark following a 7-minute adaptation period; and following vestibular activation. In each condition, subjects began by closing their eyes (30 seconds), opening their eyes and staring at the light (20 seconds), and then tracking the moving light through 20 oscillations to ensure an sample of 10 consecutive, artifact-free oscillations would be available for further analysis. The order in which subjects completed the task in the light, dark, and vestibular conditions was randomized to control for potential effects of practice or fatigue. Each condition was followed by

a rest period of 3 to 7 minutes during which the subject was engaged in conversation as preparations for the next condition were made.

Vestibular testing

Stimulation of the vestibular-ocular reflex through caloric irrigation was conducted to assess the integrity of the vestibular system in the suppression of vestibular nystagmus by ocular fixation. Prior to vestibular testing, details of the experimental procedure were reviewed with the subjects, with special emphasis on probable behavioral effects of caloric irrigation (e.g., vertigo). Reclining subjects' heads were elevated to 30° to assume the proper ventroflexed position for caloric testing. A variation of the widely accepted Fitzgerald-Hallpike technique of caloric irrigation was used (Baloh et al., 1981). Deviations from this procedure included: (a) electrooculographic recording of eye movements; and, (b) unilateral irrigation with cool (30°C) water only. Generally, warm (44°C) water irrigation is included as well, and results from additional irrigations are employed in deriving a measure of vestibular response symmetry. However, in view of the absence of asymmetry in studies of psychiatric patients (Jones & Pivik, 1985), and the potential negative motivational effects of an extended testing sequence on patients, only unilateral irrigations with cool water were used.

Water cooled and maintained at 30°C by a Grant Instruments Circulator was delivered through a double-walled hose to the external auditory canal over a 30 second period. The total volume of water delivered for each irrigation was 250ml. Eye movements were recorded continuously during the calibration, irrigation and post-irrigation intervals. While their eyes were closed, subjects performed serial subtraction by 3's throughout the procedure to maintain alertness (Collins, 1963; Cooper & Pivik, 1991). Following the initial 70 second period during

which nystagmus reaches maximum amplitude and constant slow phase velocity, subjects were instructed to open their eyes and fixate for 20 seconds on a target light, and to depress a hand-held button in response to random, brief (200 msec) signal interruptions. The pendulum-tracking task was then repeated (20 oscillations).

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test is a neuropsychological tool thought to be sensitive, but not specific to, frontal cortical dysfunction, particularly in the dorsolateral prefrontal cortex/basal ganglia circuits (Goldberg et al., 1987). This tool is thought to assess the capacity for logical category formation, and the ability to shift or modify behavior using verbal feedback provided by the examiner. The WCST was administered to all subjects individually, and scored according to standard procedures described in Heaton (1981). Each subject was provided with 2 decks of 64 cards each, and asked to place each card below one of four stimulus cards, which varied on dimensions of shape, number, and colour. No further instructions were given. Following the placement of each card, the examiner provided the subject with a 'yes/no' response to indicate the appropriateness of the card placement. The following scores were derived:

Categories Achieved (CATEG): Number of categories achieved. A category is achieved if 10 consecutive cards are sorted according to the correct sorting rule (maximum score of 6 categories using a maximum of 128 cards).

Failure to Maintain Set (FMS): Number of times at least 5 consecutive correct responses are made but the subject fails to pursue this correct sorting strategy, resulting in a failure to achieve a category.

Perserverative Responses (PR): Responses that would have been correct in the previous sorting stage (i.e., the subject continues to sort according to the previously correct category).

Perserverative Errors (PE): Perseverative responses that are also incorrect responses.

Non-Perseverative Errors (NPE): Computed by subtracting the number of perseverative errors from the total error score.

Efficiency (EFF): A new score computed specifically for this study to examine average sorting efficiency (i.e., the number of categories divided by the number of trials needed to achieve that number of categories).

The CATEG score provides useful descriptive information regarding overall success on the task, and an FMS score greater than zero serves as a specific indicator of the atypical quality of the performance. Using a perserverative response cut-off score of ≥ 19 has been shown to be the most useful in distinguishing patients with frontal lobe lesions from those with pathology in other areas of the brain, and from controls (Heaton, 1981).

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) procedures were conducted by technicians at the Ottawa General Hospital using a Siemens 1.5 Teslar Magnetom⁵. Contiguous axial (5mm), sagittal (3mm), and coronal (1.6mm) scans were obtained through the brainstem, cerebellum, lateral ventricles and frontal lobes. Highly T-2 weighted images (spin echo 440/11) were used for morphological definition. Seven millimeter contiguous T-1 weighted and T-2 weighted (spin echo 2500/40, 90 with gradient motion rephasing to reduce cerebrospinal fluid motion artifact) images were used for detection of abnormal water distribution or state as in areas of gliosis. The

total scanning time per subject was approximately 25 minutes. All subjects' images were screened by a radiologist, and no major anomalies which would necessitate a medical referral or exclusion of subjects from the study were found.

Data reduction and analysis

Pursuit tracking data

Recordings were coded and screened for the presence of artifact (e.g., electrical, blink, movement) and to ensure that the subject was directing and maintaining attention during the tracking task (i.e., detection of signal interruptions). All tracking signals were digitally filtered at 12 Hz, and corrections made for phase lag between the HEOG and the tracking signals. The first three cycles from each trial were excluded from further analysis to avoid the potential confounding effects of variability in subjects' ability to orient to the task. The next 10 artifact-free oscillations in each condition (i.e., light, dark, vestibular) were subsequently analyzed using proprietary software previously developed and used in this laboratory, for the following parameters:

- (1) The general correspondence of tracking and target patterns, indexed by the root-mean-square error deviation (RMS).
- (2) The ratio of eye velocity to target velocity [pursuit gain (GAIN)]. A score of 1.0 indicates perfect tracking, with increasingly worse tracking reflected in lower scores. Saccades were removed prior to the calculation.
- (3) The incidence of saccades (SACC). A saccade was counted when the velocity of the eye differed from the corresponding target velocity by more than $\pm 12^\circ/\text{second}$.

These measures have been widely used in eye tracking analysis, and although they may covary, they may not reflect the same processes and could therefore correlate differently with the WCST and brain imaging measures.

Vestibular data

Proprietary software was used to derive a measure of the effectiveness of visual fixation in suppressing nystagmus, known as the fixation suppression index (FSI). This index is calculated by dividing the numerator, i.e., the mean slow phase eye velocity of 10 seconds of nystagmus occurring just before the eyes are opened, minus the mean of 10 seconds of nystagmus occurring while the eyes are opened and fixating, by the denominator, i.e., the mean slow phase velocity of 10 seconds of nystagmus occurring just before the eyes are opened (Cooper & Pivik, 1991). Perfect fixation suppression will result in a value of 100%. Results were coded as complete or incomplete suppression to allow comparison of rates of purported disturbance in visual-vestibular interaction across groups.

MRI data

All MRI images were transferred from magnetic tape to optical disk for analysis on an IBM workstation. Volumetric measurements were made using proprietary image analysis software, an interactive user-driven package in which areas of interest are outlined using a mouse-driven cursor. Volumetric measurements were automatically calculated by quantification of the number of pixels enclosed in the outlined area, and multiplying this area by the slice thickness. Each area was sampled 3 times for a single average volume estimate. Two raters blind to group membership independently recorded each volumetric measurement for the first 8 subjects

analyzed, and a high level of inter-rater reliability was obtained [analysis of variance intraclass correlation: $r(1,95)=.962$, $p=.000$; reliability procedure as recommended in Bartko and Carpenter, 1976]. One rater completed the remaining measurements, with consensus achieved on questionable measurements.

INSERT FIGURE 1 HERE

Quantification of areas of interest

Frontal eye fields

A variety of procedures have been used across laboratories to examine brain abnormalities, ranging from simple visual rating scales and linear measures (e.g., width), to volumetric quantification procedures more recently. Since attempts to quantify the frontal eye fields have not been previously reported, detailed information regarding the criteria used to analyze this region of interest are provided below.

From regional blood flow studies, Melamed and Larsen (1979) found the area of the frontal eye fields to correspond to the middle third of the primary motor strip in the precentral gyrus, extending anteriorly into the posterior part of the middle frontal gyrus. Fox and colleagues (1985) gave more precise information using positron emission tomography, localizing the centre of the frontal eye fields 42mm above the commissural plane and approximately 10mm down from the surface of the anterior lip of the precentral sulcus according to Talairach's coordinate system (Talairach & Tournoux, 1988). This region has been described as ellipsoid-shaped, with

a 12mm vertical axis and a 7mm horizontal axis, with its centre at the posterior border of the middle frontal gyrus (Roland & Zilles, 1994).

For this study, the Talairach and Tournoux Atlas (1988) was used to identify the horizontal image corresponding to that presented in Fox et al (1985). Since the images taken in this plane are not marked by distinct anatomical borders, and the slices were quite thick, the corresponding coronal images were used for quantification. The coronal image marking the posterior margin of the anterior commissure (i.e., plate VCA; see Figure 1) was considered to correspond most closely to the posterior border of the frontal eye fields. This index image is easily identifiable as it is characterized by prominent structures including the lateral ventricles, optic chiasm, third ventricle, caudate and lentiform nuclei, anterior commissure, and corpus collosum. Using the dimensions discussed previously, it was estimated that 5 images (thickness=1.6mm, total 8mm horizontal distance) would capture this region in the coronal plane. For each subject, coronal slices were previewed to identify the index image, and a single circumferential measurement of the inner table of the skull was taken. This measurement (CAVOL) allowed standardization of the volumes of various brain areas by expressing them in proportional terms, and served as a means for controlling for individual variability in head size.

On the index image and the four immediately rostral images, the middle frontal gyrus was identified and circumferential measurements taken (see Figure 1). The sum of these five measurements, taken bilaterally, provided volumetric measures of the left, right, and total frontal eye field regions (i.e., LFEF, RFEF, FEF).

INSERT FIGURES 2 AND 3 HERE

Cerebellar structures

Figures 2 and 3 show the anterior vermis (lobules I to V), superior-posterior vermis (VI and VII), inferior-posterior vermis (VIII), and the fourth ventricle. In Figure 3, a midsagittal slice from a subject in the present investigation is presented, with the fourth ventricle and superior-posterior vermal areas outlined for quantification. Vermal measures were made according to procedures reported by Courchesne and colleagues (1988). In previewing the sagittal images (3mm thickness), the vermis was clearly visible on a minimum of two images for each subject. Typically, on each of these images, the aqueduct of Sylvius and the deepest extent of the primary and prepyramidal fissures were visible.

On these two images, the anterior and superior-posterior vermal lobes were outlined to obtain a whole vermal measure (VERMW). The superior-posterior lobe was outlined as in Figure 3 using the methodology of Courchesne et al (1988; i.e., a line drawn from the deepest aspect of the primary fissure to the apex of the fourth ventricle, and a second line from the deepest aspect of the prepyramidal fissure to define the upper and lower borders of this lobe; VERMP). The area of the fourth ventricle was outlined as described in Piven et al (1992; VENT4). A summary of the measurements and abbreviations used are presented in Table 1.

INSERT TABLE 1 HERE

Statistical analyses

A series of t-tests were used to compare the groups on developmental and intellectual variables. Patient symptom rating data were summarized using descriptive statistics.

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Analysis of variance procedures were used to examine the effect of group status (i.e., patient versus control) on the various measures. Data were screened for normality of distribution prior to further analyses. Non-parametric statistics were used when assumptions underlying the analysis of variance procedures were violated (i.e., Mann-Whitney U Statistic). Given the small sample size and the number of a priori directional hypotheses, primarily univariate analyses were conducted, with Bonferroni corrections for experiment-wise error applied to each cluster of variables (i.e., tracking, brain imaging, WCST). In the case of the smooth pursuit tracking data, where data were collected in three conditions (i.e., light, dark, vestibular), repeated measures analysis of variance procedures were used. Paired t-tests were performed to examine whether the groups differed with respect to the magnitude of their anticipated improvement in smooth pursuit tracking performance in the dark relative to light conditions. Generally, the significance level was set at $p < .05$, with more stringent levels applied as needed to correct for the effects of experiment-wise error.

A series of planned, exploratory, post-hoc analyses were also conducted to determine which variables would be the most powerful in distinguishing psychotic from normal adolescents, to examine the co-occurrence of dysfunction or abnormality among the patients, and to understand how distinct variable sets may be related. As equal groups of male and female patients were recruited to this study, exploratory, post-hoc analyses of the data by gender were conducted.

RESULTS

Virtually all patients were diagnosed as schizophrenic at the 6 month follow-up (11/12; 1 schizoaffective) and the majority of patients were receiving medication at the time of testing

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(8/12; 6 were receiving phenothiazines alone, 1 also received pimozide; 1 received risperidone alone). Patient symptom rating information is summarized in Table 2. All patients scored within the range expected for outpatients (Endicott et al., 1976; Branff et al., 1991). Tanner sexual developmental ratings were similar for the two groups [$\bar{x}$ (SD): patient, 4.5(.44); control, 4.4(.47); $t(23)=0.28$, ns]. Intelligence scores were significantly higher in the control group [$\bar{x}$ (SD): patient, 101.2 (13.6); control=118.7 (10.2); $t(23)=3.41$, $p<.01$].

INSERT TABLE 2 HERE

Tracking and WCST data were analysed from the 12 patient and 12 control subjects. MRI data were not available for one male patient due to his premature departure from hospital, and consequently the matched control subject's brain imaging data were examined but not included in the statistical analyses to maintain equality of group size.

Smooth pursuit tracking performance

The results of group comparisons of smooth pursuit tracking data are summarized in Figure 4. Separate analyses were conducted for each index measure (i.e., GAIN, RMS, SACC) to evaluate the effects of condition (i.e., light, dark, vestibular) by group (3 x 2 ANOVA's). No interactions of group by condition for any of the tracking indices were found. There was an expected main effect of condition on each index, with the best performance evidenced in the dark. There was a surprising *lack* of significant group differences on all indices of smooth pursuit tracking quality across the three conditions.

INSERT FIGURE 4 HERE

Fixation suppression

Four patients displayed incomplete suppression of the evoked nystagmus response through visual fixation, whereas all of the control subjects showed complete suppression (patient #3, 85.9%; #5, 45.9 %; #6, 15.5%; #11, 23.9%; $\bar{x}$ = 42.8%). Using the Mann-Whitney U test, a significantly higher rate of fixation suppression difficulty in the patient group was observed ($df=12,12$; $U=48$, with correction for ties, $p<.05$). Follow-up analyses revealed that the four patients who displayed incomplete fixation suppression showed worse tracking in the light condition relative to all other subjects (GAIN and RMS ($df=4,20$; GAIN $U=15$, $p<.05$; RMS $U=5$, $p<.01$; SACC $U=18$, $p=.09$). Greater improvements across light to dark conditions were also observed (i.e., calculated by subtracting each subject's score in the dark condition from the score in the light condition, ($df=4,20$; GAIN improvement $U=15$, $p<.05$; RMS improvement $U=6$, $p<.01$; SACC $U=20$, $p=.10$).

MRI data

Quantitative evaluation

No significant group differences were found on any of the brain imaging measures (see Table 3). A trend towards smaller absolute left (LFEF, $p=.10$) and total (FEF, $p=.11$) frontal eye field volumes in the patient group was weakened when the measurements were expressed as proportions of the total volume on the index image (FEFPPR, $p=.21$). The patient group mean

for the absolute whole vermis measurement was also somewhat smaller than that for controls (VERMW, $p=.18$).

INSERT TABLE 3 HERE

Performance on the WCST

As screening of the WCST data revealed that the assumption of homogeneity of variance between the groups was not met, the Mann-Whitney U statistic was computed for all WCST performance indices. Results of the between-group comparisons on the various indices are presented in Table 4. Due to the number of comparisons made, group differences were evaluated using a stringent significance level (i.e., $p<.05/6$ or $p<.008$).

As expected, the performance of patients on the WCST was significantly poorer than that of the control group. All control subjects obtained perfect scores with respect to the number of categories achieved (CATEG), compared to only 58% of the patient group (i.e., 7 of 12). Failure to maintain set (FMS) was almost exclusively demonstrated by the patient group (8/12 or 67% of the patient group displayed at least one FMS, with no subject displaying more than 2, compared to 1 control subject). Patients also consistently obtained significantly higher perservative response measures, i.e., PR, PE, and NPE scores. The efficiency of their performance (EFF) was also impaired relative to the control group.

INSERT TABLE 4 HERE

Subsequent analyses revealed that WCST performance was not significantly correlated with intelligence ratings in either the patient ($r = -.008$, $p = .98$) or control groups ($r = -.31$, $p = .32$). In an exploration of which of the WCST indices would be most useful in discriminating between groups, a logistic regression analysis was conducted. All WCST indices that yielded non-zero scores (i.e., PR, PE, NPE, EFF) and IQ scores were included. The results of the analysis revealed that the PR score was the most effective index in this regard [i.e., classification rate of 75% (9 of 12) for the patient group; 91.7% accuracy (11 of 12) for the control group; 83.4% overall accuracy].

Post-hoc analyses

Visual (non-automated) ratings of smooth pursuit tracking performance

To further investigate the surprising absence of group differences on all indices of smooth pursuit tracking, the polygraphic records for all subjects were reviewed by visual examination. Many of the records suggested disordered tracking of the nature reported in previous studies. A visual rating evaluation of the tracking data was therefore conducted to assess whether the lack of difference was due to both groups being similarly impaired on this task. Coded light and dark recordings were examined and rated by two independent raters, who had established a high degree of reliability (i.e., 96% agreement on a sample of 20 records collected in a previous study involving adult controls and schizophrenic patients), using an expanded version of the dichotomous Benitez scale (1970: see Appendix A). On this scale, ratings ranged from normal ("0") to extremely abnormal ("5"), and were subsequently collapsed into two categories (i.e., normal "<2" versus abnormal " ≥ 2 ") to allow for comparison of the results with other studies that

have used the Benitez scale. A high level of inter-rater agreement was obtained for the current data (i.e., 95.8% agreement, based on 48 ratings, light and dark conditions only).

Results of chi-square analyses using the dichotomous ratings confirmed that the groups did not differ with respect to the quality of their tracking (χ^2 light = .20, df = 1, ns; χ^2 dark = .17, df = 1, ns). However, both groups had similar proportions of “abnormal” ratings which were reduced in the dark relative to the light condition [i.e., light: patients = 75% (9/12), controls = 66.7% (8/12); dark: patients = 58.3% (7/12), controls = 50% (6/12)].

The associations between the visual ratings of tracking performance and the quantitative measures were assessed with a series of Spearman correlations on data from the the light condition. As expected, visual ratings and computer-quantified scores were correlated to a significant degree in the anticipated direction [r GAIN = -.57, p = .002; r RMS = .55, p = .003; r SACC = .64, p = .0004).

Data from a patient sub-group with impaired WCST performance

A sub-group of 6 patients with poor performance on the WCST was identified for further analysis using the clinical cut-off for frontal brain injury as reported in Heaton (1981). This group included the one subject for whom MRI data were not available. The MRI and eye movement data obtained from this sub-group were compared to those of the other patients and the controls using logistic regression analyses. Interestingly, the combination of absolute volumetric measures of the frontal lobes (i.e., FEF, LFEF, RFEF) was most useful in distinguishing this group from the rest of the sample (94% accuracy, 17 of 18, for those not in the sub-group; 60%, 3 of 5 for the frontal sub-group (1 missing; 87% accuracy overall; optimal

$\chi^2=11.98$, $df=4$, $p<.05$). The symptom ratings for this sub-group did not differ significantly from those of the other patients. Two members of this sub-group verbalized the correct WCST sorting procedures, but failed to modify their response patterns accordingly. Four of these 6 patients also showed abnormal tracking according to the visual ratings analyses.

Co-occurrence of abnormal ratings/performance

Table 5 presents patient information comparing ratings and performance across individual cases. Inspection of these data reveals no clear one-to-one co-occurrence among the variables of interest. However, 4 patients showed both impaired tracking and impaired WCST performance. If the data from two patients whose PR scores were very close to the suggested cut-off for frontal brain pathology were considered in addition to those who met or surpassed the cut-off level, the correspondence with tracking impairment increased from 67% to 75% (i.e., 4 of 6 and 6 of 8, respectively). The rate of tracking impairment in the control group was also high, but was not associated with impaired WCST performance. No clear correspondence between WCST performance and the ranked frontal lobe MRI data was apparent in the patient group.

Of the four patients with abnormal fixation suppression, two were among those with the smallest vermal measurements in the patient group. One showed impaired (#11), and the other (#3) showed nearly-impaired WCST performance. The other two (#5 and #6) showed both impaired WCST and tracking performance, with one showing consistently smaller frontal measurements (#6).

INSERT TABLE 5 HERE

Bivariate correlations

Due to the small number of subjects relative to the number of indices, only bivariate comparisons between the sets of variables were conducted. A stringent significance level ($p < .001$) was used to compensate for the large number of comparisons made. When scores on the WCST and tracking tasks were subjected to correlational analyses, the strongest and most consistent correlations were found between RMS and PR, such that better tracking (i.e., lower RMS) was associated with a lack of perseveration. However, the correlation approached statistically significant levels only when the RMS data from the dark condition were used ($r = .50$, $p = .007$).

A number of low level correlations were obtained between various MRI measures and smooth pursuit tracking or WCST performance indices. Only the correlation between GAIN and fourth ventricle size (VENT4) in the vestibular condition approached statistically significant levels ($r = .58$, $p = .005$).

Gender

A series of 2 X 2 ANOVA's were used to examine gender effects, and the possible interaction of gender by group, for all dependent measures. These analyses revealed a lack of significant interaction effects of gender by group on all eye tracking, brain imaging, and WCST indices. Females had slightly lower gain scores than males across conditions ($p < .09$), slightly larger proportional posterior vermal scores ($p < .08$), and slightly larger fourth ventricle scores ($p < .10$).

DISCUSSION

The main goal of this investigation was to determine whether smooth pursuit tracking performance deficits which have been shown in older schizophrenics would be present in adolescents experiencing their first psychotic break, and whether volumetric brain measurements of the areas implicated in smooth pursuit control (i.e., frontal eye fields and cerebellar vermis) would show reductions in these patients. Functional integrity of the frontal lobes and the cerebellum, as indexed indirectly using the WCST and the vestibular activation paradigm, respectively, was also examined in anticipation of impairments in the schizophrenic subjects. Major strengths of the study included the use of a multiparameter approach and the specific focus on a young group of schizophrenic patients. The importance of restricting the study to this age group (i.e., not combining adolescents with older individuals experiencing their first break) is clear when one considers that as many as 39% of individuals diagnosed with schizophrenia have symptom onset before age 20 (Findling et al., 1995), and that earlier onset has been shown to be related to less favourable clinical outcome (Gillberg et al., 1993).

The most serious limitation of this study was the small sample size, which may compromise the degree to which these data can be considered representative of the range of pathology in early psychosis. However, the symptom ratings suggest a similar level of pathology relative to outpatient psychiatric patients and were generally within the range reported in studies of older subjects. Despite the small sample size, a number of significant results were observed and the utility of the data was maximized by detailed case analysis of the co-occurrence of abnormalities – an uncommonly practiced approach which proved useful as a complement to group data analysis techniques.

Tracking performance

Of the findings reported, perhaps the most surprising was the *absence* of group differences on all quantitative indices of smooth pursuit tracking. This finding did, at first glance, suggest a lack of disordered tracking in psychotic adolescents. However, this conclusion was not supported by further visual inspection and rating of the smooth pursuit recordings, which revealed a higher than expected proportion of disordered tracking in the control group. Fully one-half of the control adolescents displayed consistently disordered smooth pursuit tracking across conditions according to the visual ratings -- a rate considerably higher than the 5 to 8% reported in studies using older controls (Holzman et al., 1973, 1974a; Iacono et al., 1992).

Two issues arise from this finding. First, there is the methodological issue of how to define and evaluate disordered tracking. Clearly, reliance on group analyses of computer-assisted quantitative data alone in this study would have provided an incomplete assessment of tracking performance, since there are no standardized guidelines to facilitate the interpretation of the quantitative data outside of group comparisons (e.g., no standard cut-off for 'abnormality'). A more complete and valid interpretation of the data was facilitated by the addition of the visual ratings assessment method. However, it must be noted that despite the wide use of rating scales and their practical applicability to categorizing the tracking data, they have not been subjected to rigorous psychometric evaluation.

The solution to this methodologic issue would appear to be a strategy that links the categorical rating scales with the numerical data. Such an approach would facilitate the comparison of quantitative results across studies, and would also allow for the categorization of individual subjects into subgroups based on the presence or absence of dysfunction, thereby

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providing a better understanding of the rate of pathology within the groups. Normative data covering as great an age range as possible would be very helpful in making determinations about pathology, as there is preliminary evidence to suggest that tracking ability deteriorates with increasing age (Kuechenmeister et al., 1977). A useful first step in this process would be the re-examination of data from completed large-scale studies (e.g., Iacono et al., 1992) relating rating scale results to those obtained by electronic and computer processing. Scales validated in this fashion, and whose psychometric properties have been fully evaluated, might facilitate the process of screening for, or monitoring change in, tracking dysfunction (e.g., at-risk groups, other psychiatric or neurological populations). Clearly, the association between quantitative and visual ratings data in this study -- a result which is consistent with the data on older patients and controls (Friedman, et al., 1995a) -- provides an empirically-based rationale for the development of such an approach.

The second issue arising from the visual ratings of tracking performance relates to the implications of the surprisingly high rate of disordered tracking in both the patient and control groups. The rate of disordered tracking found in this first-episode, adolescent patient group [i.e., 75% (light condition)], was slightly higher than that reported in a group of older, first-episode patients (e.g., 51%, using the Benitez rating scale, illuminated conditions, as reported by Lieberman et al., 1993) and considerably higher than the 20% reported by Iacono and colleagues (1992) using conservative, probabalistic methods to determine deviance (i.e., RMS values that exceeded the control mean by 2 standard deviations; $\bar{M}$ age=23 years). The lack of group differences suggests that poor tracking is not specific to psychotic individuals in this age group.

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In order to interpret this result, reasons for the high rate of disordered tracking in normal adolescents (i.e., 67%, light condition) must be considered.

Normal subjects have shown tracking difficulties similar to those identified in this study under a variety of conditions. These include anxiety-provoking conditions (e.g., threat of electric shock) or conditions designed to increase boredom or fatigue, thereby reducing arousal and attentional resources (Brezinova & Kendell, 1977). In the present study, the poor performance of the control group could not be explained in terms of anxiety, and there was strong evidence indicating that they remained alert and vigilant throughout testing (i.e., as indexed by their performance on the attentional task). However, the control group, similar to the patient group, also displayed some tracking improvement in the dark condition, which may implicate central attentional processes sensitive to the reduction in distracting stimuli with the removal of ambient light. One viable explanation for these results is that systems involved in smooth pursuit, and perhaps basic information processing systems more generally, have not yet reached adult performance levels, perhaps indicating a performance deficit based on maturational factors. Support for this hypothesis comes from the results of a recent study of the normal development of oculomotor functioning indicating inferior performance of pre-adolescent males (i.e., 11-12 years) to those in late adolescence (i.e., 17-18 years) and adulthood (i.e., 34-63 years; Katsanis, Iacono, & Harris, 1998). The authors concluded that, on average, tracking performance reached adult levels in late adolescence; considerable variability was, however, evident within each of the age groups such that not all subjects in the late adolescent age group could be considered to be performing at adult levels. The average age of the controls in this study was 17.05 years, but ranged from 14 through 19, suggesting that the results should be roughly comparable to the

performance of Katsanis and colleagues' late adolescent group (i.e., exclusively 17-18 year olds). On average, the RMS and gain scores in the Katsanis et al study, which appeared to be quantified using methods similar to those used in the present investigation, were somewhat better than those reported here, for both the late adolescent and adult groups. On average, pre-adolescent males demonstrated inferior performance relative to the subjects in the current study. Generally, the results of the current study are consistent with the Katsanis et al study, and with other investigations showing incomplete development of smooth pursuit functioning in younger adolescents (Accardo et al, 1995; Ross et al., 1993).

The lack of group differences found in this study are, however, in contrast to those found by Gordon, Jacobsen, and colleagues (1994, 1996), who found childhood schizophrenia patients to differ from normal peers on eye tracking performance. Unfortunately, these results, based on a patient group with childhood-onset schizophrenia diagnosed on average 4 years previous to testing and taking clozapine, are not directly comparable to the results obtained in the current study (i.e., adolescent onset, early in the course of their illness, and not taking clozapine). Of interest, however, is the similarity in the average gain results and the observed variability for the patient groups in both studies. The average gain results for the normal controls in the childhood-onset study were slightly better than those of the adolescent controls in the current study, although again there was considerable variability, with a great deal of overlap in the values obtained.

In summary, it appears that high rates of poor tracking in adolescence may be expected as part of a normal developmental course, with significant improvement anticipated in the majority of these individuals as they reach adulthood. Longitudinal studies would greatly facilitate

understanding this developmental progression, and would provide information regarding when smooth pursuit tracking performance can reliably be used to discriminate normal from psychotic individuals. Studies with larger samples of both young controls and schizophrenic patients are clearly required to fully address this issue. However, the high rates of poor tracking in the patient group in this study, and the high rates found in adult samples, strongly suggest that a portion of the psychotic adolescents will continue to show disordered tracking well beyond their adolescent years. These data provide suggestive support for the hypothesis of a developmental dysfunction or arrest in the maturation of the systems implicated in smooth pursuit in schizophrenia.

Volumetric brain measurements

Group analyses of volumetric brain measurements also did not reveal differences between the patient and control adolescents. Among the several possible interpretations of this result is the hypothesis that volumetric differences in the specific regions examined do not exist, even in the presence of functional disturbances (e.g., as suggested by functional imaging studies of the frontal lobes generally; Velakoulis & Pantelis, 1996). Another possible explanation of these negative findings on group analyses relates to the limited power when using a small sample size to detect small differences which may exist between the groups. However, both functional and structural imaging studies of the brains of schizophrenic patients and normal controls have revealed group differences using similarly small sample sizes (Nopoulos, Torres, Flaum, Andreasen, Ehrhardt, & Yuh, 1995; O'Driscoll, Alpert, Mattysse, Levy, Rauch, & Holzman, 1995). Interestingly, in reviewing the data obtained in the current study and calculating effect

sizes for the MRI results approaching significance, only 4 additional subjects displaying similar results to the existing subjects would have contributed to a significant finding with respect to differences in the left frontal eye fields (19, for total frontal eye fields; 32 for the whole vermis measure). Clearly, similar studies of these brain areas in larger samples are needed to address this issue.

Another consideration relates to the method of measuring the areas of interest. Although care was taken to reliably measure the regions of interest, it remains possible that sites of pathology, and potentially the sites of volumetric differences, lie outside of the measured area. The lack of empirically-based guidelines with respect to standard procedures for obtaining and reporting volumetric measurements of the frontal eye field area in particular makes it difficult to dismiss this possibility. A final interpretation of these findings is suggested by the exploratory analyses, i.e., volumetric differences do exist between patient sub-groups and controls, but are masked by group analysis of the data alone.

The hypothesis that the frontal eye field region might be reduced in patients was derived from a logical analysis of the eye tracking literature, implicating this area in smooth pursuit control, and extrapolated from the results of functional imaging studies (Rubin et al., 1994; Batista et al., 1995; Velakoulis & Pantelis, 1996), a small number of studies suggesting volumetric differences in a nearby area (i.e., dorsolateral prefrontal cortex; Seidman et al., 1994), and in frontal regions generally (Lieberman et al., 1993; Andreasen et al., 1986; Napoulous, Torres, Flaum, Andreasen, & Ehrhardt, 1995; Woods, Yurgelun-Todd, Goldstein, Seidman, & Tsuang, 1996). Negative findings of volumetric differences have been reported, however, in both schizophrenic patients (Andreasen et al., 1990) and in children at-risk (Hendren et al.,

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1995). Unfortunately, the rate of frontal abnormality in imaging studies is unclear, as it has only rarely been reported. Andreasen and colleagues (1986) reported that approximately 40% of their sample had smaller frontal lobes and decreased cranial size (i.e., a large sub-group), but this result was not replicated in their 1990 study. Lieberman and colleagues (1993) reported that approximately one-third of their sample of 66 first-episode patients showed some evidence of brain involvement, including, but not restricted to, the frontal/parietal region, with a large number of patients showing 'questionable' abnormality in this area. Despite the lack of data regarding the rate of frontal structural/volumetric abnormality in schizophrenia, it is clear that frontal abnormalities would be expected in some, but not all, cases of schizophrenia. Therefore, it was not surprising to find only a sub-group of patients with possible frontal lobe involvement in the current study. Similarly, the lack of group cerebellar differences may be viewed as the result of only a few subjects showing abnormality in this brain region, which would also be consistent with the equivocal findings of the few studies to have examined possible cerebellar involvement in schizophrenia (Weinberger et al., 1979; Heath, Franklin, & Shraberg, 1979; Yates et al., 1987; Nasrallah et al., 1991; Alyward et al., 1994).

Although no group differences emerged in the MRI data, exploratory analyses implicated both frontal eye field and cerebellar vermal regions in two sub-groups of patients in the current investigation. Smaller frontal eye field areas were found in a group of patients demonstrating impaired WCST performance, the implications of which will be discussed later in this paper. A second group of 4 patients demonstrated a cluster of performance deficits similar to that found by Cooper and Pivik (1991), i.e., incomplete fixation suppression suggesting disruption of the interaction between the visual and vestibular systems, and the combination of poorer tracking in

illuminated conditions with greater improvement in the dark, suggesting pathological cerebellar involvement (Alpert, 1974; Baloh et al., 1981) which diminishes under dark conditions. In addition to these indirect indices of subcortical involvement in the tracking impairment, two of these patients were among those with the smallest measured cerebellar vermal volumes in either group. These results are intriguing in terms of proposing a schizophrenia sub-group with possible cerebellar involvement, but caution is warranted as definitive localization of the brain area responsible for these difficulties remains problematic, e.g., both fixation suppression and smooth pursuit difficulties have been shown to co-occur in patients with evidence of either cerebellar or cerebral impairment (Zee, 1977), and fixation suppression abnormalities have also been identified in patients with parietal and fronto-parietal tumours (Takemori et al., 1979). Clearly, the combination of smooth pursuit, fixation suppression, and imaging measures may prove useful in future studies to further explore the hypothesis of cerebellar vermal involvement in schizophrenia.

WCST performance and possible frontal lobe involvement

Scores on the WCST were particularly useful in discriminating between the patient and normal groups. This was a particularly robust finding given the small sample size. The relatively poorer performance of the patient group was consistent with previous reports of impairment in older, first-episode patients (Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992; Chen, Lam, Chen, Nguyen, & Chan, 1996), in children thought to be at-risk for schizophrenia (Hendren et al., 1995), and in adult samples (Fey, 1951; Matsushima et al., 1992). The finding

that WCST performance was independent of general intellectual functioning also was consistent with previous reports (Fey, 1951; Goldberg et al., 1987; Matsushima et al., 1992).

The identification of a sub-group of patients with perseveration scores in the range associated with frontal brain pathology was of particular interest. Moreover, when the data were re-examined to establish which variables would discriminate this group from the remaining sample, only the absolute FEF indices emerged as useful in this regard. A link between impaired WCST performance and smaller FEF areas was therefore suggested, possibly implying a common underlying pathology for both poor WCST performance and poor tracking. The possibility of a such a link was also supported by the observation that 4 of the 6 patients in this sub-group had abnormal tracking ratings, and a weak, positive association between RMS and PR scores was found in the overall analyses. A similar association was also found in a study by Litman et al (1991), suggesting that similar processes might be contributing to impaired tracking and WCST performance. The results from several other studies also support a general association between poor tracking and poor frontal lobe functioning (Friedman et al., 1996; Volkow, Wolf, Van Gelder, Brodie, Overall, Cancro, & Gomez-Mont, 1987; Radant, Claypoole, Wingerson, Cowley, & Roy-Byrne, 1997).

The finding of impaired WCST performance in the patient sub-group is consistent with indications of frontal involvement in schizophrenia. Strong evidence exists to support a specific association between perseveration, which was the most robust index in differentiating the groups in this study, and frontal lobe pathology (i.e., specifically the dorsolateral prefrontal cortex; Milner, 1963; Luria, 1973; Drewe, 1974; Rubin et al., 1991, 1994; Seidman et al., 1994; Kertesz et al., 1997), and with lesions in either the frontal cortex or basal ganglia, which disrupt frontal

cortex - basal ganglia interactions (Eslinger & Grattan, 1993). Interestingly, perseveration is often seen alongside disinhibition in frontal lobe pathology (for a review, see Passler, Isaac, & Hynd, 1985), and it has been suggested that the smooth pursuit tracking disorder might also represent a more global disorder of inhibition (e.g., inability to inhibit incorrect or anticipatory responding, poor selective attention), which may also explain the finding of poor performance on the antisaccade task demonstrated by some schizophrenic patients (Mather, 1986, 1989; Katsanis et al., 1998, Fukushima et al., 1990; 1994). One can speculate that the apparent improvement in eye tracking performance from childhood to adulthood (Katsanis et al., 1998) may be, in part, attributable to the development of inhibitory/ attentional systems which are thought to underly a number of functions subserved by the frontal lobes (as studied by Passler et al., 1985).

Consequently, poor tracking in the controls may be interpreted as reflecting the late stages of the normal development of required attentional systems, while processes governing the development of cognitive capacities required for their good performance on the WCST have presumably already reached adult levels (i.e., in contrast to the patients).

Beyond the high level of perseverative responding identified in the patient sub-group, two other aspects of the patient group's performance on the WCST also appear to implicate frontal lobe or associated pathway involvement. Two of the patients in this study verbalized correct sorting strategies but failed to act accordingly, and 8 failed to persist with successful sorting strategies in the presence of unequivocal (i.e., yes, no) verbal feedback. Individuals with frontal lobe lesions have shown this dissociation between speech and action (Goldberg et al., 1987). Lesions in this area are generally thought to disturb the regulatory function of speech, such that the individual can no longer control his/her behavior with their own or another person's speech

(Luria, 1973). In this context, the failures to maintain set may be viewed as an example of the inability to effectively use the verbal feedback that was provided as the task progressed.

Generally, the failure of this verbal regulatory function, particularly with respect to inability to effectively integrate information to produce meaningful behavior, may explain disordered planning, organizing, and monitoring behavior in frontal lobe patients (Petrides & Milner, 1982), and perhaps in schizophrenia. Interestingly, young children demonstrate a similar phenomenon as they struggle to develop internalized language systems, which in turn facilitates the development of abstract thinking.

Defects in the interconnective pathways between the frontal lobe and other brain areas have been proposed to account for a wide range of findings in schizophrenia. A frontostriatal defect has been postulated to explain the relative lack of frontal regional cerebral blood flow activation (rCBF) in first-episode schizophrenia during WCST performance (Rubin et al., 1991; 1994). The deficit is thought to result from the inability of the prefrontal cortex to reduce striatal activity due to a lack of corticostriatal feedback during prefrontal activation (Rubin et al., 1991). A similar defect has also been proposed to account for rCBF patterns in never-medicated patients during a task of sustained, selective, visual attention requiring motor response (Buchsbaum et al., 1992). The relationship between movement disorders in those with schizophrenia and so-called "sub-cortical" dementia similarly has been interpreted as a disorder of this pathway system (Brown, White, & Palmer, 1992).

Understanding schizophrenia as a disorder of the frontal lobes and its interconnective pathways, at least in a sub-group of patients, appears to provide a parsimonious framework to account for the diversity of deficits associated with this disease. There is strong evidence for the

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existence of a number of parallel, fundamental circuits which are thought to connect the frontal lobe with deeper structures (Alexander, DeLong, & Strick, 1986). The prefrontal cortex, in particular, receives inputs from all major sensory afferent systems, with reciprocal projections allowing the prefrontal cortex to act upon these systems, in addition to limbic, diencephalic and mesencephalic structures (Teuber, 1972, as reported in Passler et al., 1985). In particular, there is a close functional interaction of frontal cortex with limbic structures in the mesial temporal lobe (e.g., amygdala and hippocampus) which appears to play critical roles in response flexibility, multidimensional association of sensorial stimuli, memory, and motivational states (DeLong, 1992). Therefore, it is not surprising that a range of disturbances of cognition, behavior, and emotion might result from damage or inappropriate development of this area and its interconnective systems. Also of interest is the observation that many of the discriminating positive and negative symptoms reported in frontal lobe dementia (i.e., perseveration, disinhibition, inappropriateness, impulsivity, irresponsibility, loss of insight, indifference, distractibility, personal neglect, apathy; Kertesz et al., 1997) appear to be similar to those commonly associated with schizophrenia. Furthermore, hallucinations and delusions have been viewed as the result of dysfunction in the frontal-temporal-limbic circuit, specifically resulting from the failure of prefrontal control over limbic function during times of stress (Hirsch, 1988). The resulting over-activity of dopamine activity has been supported in animal studies in which prefrontal lesions have resulted in disinhibition of dopamine systems in the nucleus accumbens and striatum (Hirsch, 1988). This disinhibitory function would also be consistent with the finding that both adolescent and adult schizophrenics appear to manifest a dysfunction in their ability to regulate stimulus input, resulting in anxiety (Stein, Elliot, & Offutt, 1985; Venables,

1983), rather than displaying a tonic state of hyper- or hypoarousal. Interestingly, dysfunction of forebrain-mediated inhibitory processes has also been postulated as fundamental to the understanding of Attention Deficit Disorder (Rosenthal & Allen, 1978). Prefrontal connections to *cerebellar* regions have also recently received attention in understanding subtle cognitive abnormalities in schizophrenia (see Andreasen et al., 1996).

Integration and conclusion

The results of the current investigation underscore the importance of considering smooth pursuit tracking deficits within a developmental context, specifically with respect to the need to define what can be considered 'normal' tracking at different ages. The results of the exploratory analyses suggest that the most robust finding, i.e., the group differences on the WCST, may be particularly useful in defining patients who may display frontal involvement early in the illness. A similar utility is suggested for the use of caloric irrigation in assessing fixation suppression, and the identification of patients with possible early cerebellar involvement.

As the results of the few published studies of normal subjects would suggest, smooth pursuit tracking ability appears to follow a developmental course, with tracking improving significantly over the adolescent years. The rates of disordered tracking in the controls in the current investigation were much higher than that reported for older controls, which would appear to be consistent with the interpretation that smooth pursuit tracking ability had not reached adult levels in a number of control subjects. The high rate of tracking impairment displayed by the patients in this study was generally consistent with studies of adult patients, suggesting that a portion of these adolescents will most likely continue to show impaired tracking into adulthood. The

present results, when viewed in combination with the high rates of disordered tracking in adult schizophrenia and in normal children, are consistent with a maturational influence in schizophrenia pathology. The current WCST results, when viewed in the context of studies of frontal lobe function in children, also suggest an arrest in normal development in schizophrenics showing impaired performance. In addition to these performance impairments, indications of brain structural differences in some patients at this early stage in their illness also can be interpreted as evidence of neurodevelopmental encephalopathy in schizophrenia, as proposed by Weinberger (1995).

In his review of the literature, Wienberger (1995) interpreted several consistent findings as evidence of pathological neurodevelopment in schizophrenia. These include: increased frequency of minor physical anomalies, obstetric complications, and prenatal exposure to viruses; pre-morbid cognitive and neuromotor abnormalities; non-progressive morphological deviations on neuroimaging (i.e., ventricular volume); morphological deviations without gliosis in necropsy studies; and cytoarchitectural abnormalities in histological studies. In particular, the absence of gliosis provides strong evidence against a neurodegenerative disease process and for neurodevelopmental dysgenesis. A particularly provocative finding discussed by Weinberger is the apparent cell migrational pathology resulting in a defect in the formation of the cortical plate. Necropsy studies have shown a tendency for laminar distribution of cortical neurons (e.g., in prefrontal and temporal areas) to be displaced inwards at deeper tissue levels. Nerve cells migrate outwards from the periventricular area towards the cortical surface. Due to the inside-out migration pattern, with deeper layers set down first, neuroblasts must be guided appropriately by glial fibres, and then detach from these fibres in order that subsequent neuroblasts may move

beyond (Rakic, 1988). As neurons normally migrate during the second trimester of gestation, this may prove a critical time in the disease process of schizophrenia. A migrational disorder of this nature might explain deviations in both tissue architecture and circuitry (Weinberger, 1995).

The prenatal period may be one of at least two critical periods contributing to the development of schizophrenia pathology. The possibility of an early disruption in development is supported by evidence of neurointegrative disorders in children at risk for developing schizophrenia [e.g., depressed arousal (i.e., gross motor, vestibular), failures of midline bimanual skills, deficits in the focussed attention and organizational aspects of visual-spatial perception], some of which can be observed as early as in infancy (Erlenmeyer-Kimling & Cornblatt, 1987; Fish, 1987; Marcus et al., 1987; Shapiro, 1993). In addition to this early disruption (e.g., a cell migration disorder), schizophrenia, or sub-groups thereof, may also be characterized by disease progression during the adolescent years. This period of significant neurodevelopmental change may result in further pathology resulting from faulty myelination of pathways (Benes, 1989), and/or faulty programmed synaptic elimination (Feinberg, 1982). It is also possible that these processes may themselves be intact, but appear to be pathological because the normal processes are allowing the early defect to be detected. For example, if cells have migrated to inappropriate areas, a normal process of programmed synaptic loss for a specific region may have unpredictable results. Myelination of inappropriately constructed pathways may have similarly pathological effects. Interestingly, the brain area thought to be responsible for poor WCST performance (i.e., the dorsolateral prefrontal cortex) is both one of the most recent to develop in evolutionary terms, and one of the last to mature in humans (Bachneff, 1991). Myelination of

this area is virtually non-existent in subprimate species, and the myelination process in humans is not complete until the second or third decade.

In general, if schizophrenia is considered to be the result of developmental neuropathology, a range of clinical presentations and outcomes would be expected in addition to a diversity of research outcomes with respect to neuropsychological, neurophysiological, and neuroimaging variables. Also, some neurological changes may be observable at the onset of the illness, whereas others may occur later in the course of the illness (DeLisi et al., 1991) – a suggestion which may also hold for our understanding of the neuropsychological deficits in this population. The presence of negative findings and the identification of sub-groups would also be anticipated.

The results of this study clearly do not support the use of smooth pursuit tracking in discriminating schizophrenic adolescents from controls, and they attest to the need to examine purported tracking impairments within a developmental framework. Some insight was provided into the need for a more rigorous, standardized approach to defining and assessing eye tracking dysfunction, and the interpretive limitations of group data analyses were highlighted. The general lack of volumetric differences between groups on measures of the frontal eye fields and cerebellar vermis suggest that differences, when they exist, may be most likely to be identified in sub-groups of patients. The positive finding of impaired WCST performance in a sub-group and the generally impaired performance of the patient group relative to controls, confirm the usefulness of this tool in the study of adolescent schizophrenia. Clearly, the results presented here suggest that defining sub-groups, particularly those based on the performance on simple, functional neuropsychological tests, may provide an appropriate, sensitive approach to understanding and integrating data from a range of paradigms.

This study was unique in terms of the population studied (i.e., mixed gender group of adolescents experiencing their first psychotic break) and the diversity of dependent measures employed. It is the first to present a methodology for the volumetric measurement of the frontal eye field region, the reliability and validity of which will need to be assessed in future studies. Data analyses were not limited to the examination of group differences, but also included an exploration of the co-occurrence of abnormalities in individual patients across a range of measures -- an approach not previously reported in the published literature. Follow-up studies of larger samples of adolescents are recommended using a variety of well-validated tools and standardized assessment procedures. In particular, functional imaging approaches, in combination with the measures employed in this investigation, may be particularly useful in advancing knowledge about the co-occurrence of impairments in schizophrenia. Mixed-gender samples will also be important, as the majority of information about schizophrenia is based on studies of males alone (Iacono & Beiser, 1992). Clearly, future research should be guided by theoretically-driven hypotheses, perhaps related to the neurodevelopment theory of schizophrenia, to build more systematically towards a better understanding of this disease.

NOTES

¹ Interestingly, a link with low birthweight has been suggested (Silverton, Mednick, Shulsinger, Parnas, & Harrington, 1988).

² Enlarged ventricles have also been found in other psychotic patients (Rieder, Mann, Weinberger, van Kammen, & Post, 1983; Andreason, Swayze, Flaum, Alliger, & Cohen, 1990a), and may be more common among male than female schizophrenics (Flaum, Arndt, & Andreasen, 1990).

³ Numerous three-neuron arcs connecting the vestibular end organs to the extraocular muscles effect this compensatory reaction. The medial longitudinal fasciculus, the brachium conjunctivum, and the ascending tract of Deiters' are the main pathways involved in these interactions (Highstein & Reisine, 1979)

⁴ Smooth pursuit and visual suppression of the VOR are thought to share a common pathway at least to the level of the cerebellum. Anatomical and functional dissociation of the signals mediating the two functions are proposed to account for the observation that some patients display selective impairment of one or the other systems. Lesions of the flocculus alone impairs both functions (Chambers & Gresty, 1983).

⁵ MRI has several advantages over other scanning techniques (e.g., computed tomography, CT). MRI does not use radiation or intravenous iodinated contrast agents, making it safe for repeated use, and enhancing the possibility of attracting a less biased sample of comparison subjects (Cohen, Buonanno, Keck, Finklestein, & Benes, 1988). Multiplanar images (e.g., sagittal, coronal and tranverse) are obtained without moving the patient (Conlon & Trimble, 1987). The white to grey matter contrast is also superior (Norman & Brant-Zawadski, 1985), with overall morphological detail enhanced as discrimination of tissues is based on their physical and biochemical properties (water, iron, fat, intra- and extra-vascular blood, and breakdown products; Sachdev, 1990). Because calcium does not emit a signal on T-2 weighted images, magnetic resonance images of the cerebellum, subcortical structures, brainstem and temporal lobes are not obscured by bone artifact (Garber, Weilburg, Buonanno, Manschreck, & New, 1988).

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Table 1: Summary of MRI measurements and abbreviations

“Absolute” volume measurements (expressed in cm³)

Index of Brain Volume	CAVOL
Frontal Eye Fields (Left, Right, Total)	LFEF, RFEF, FEF
Superior-Posterior Vermis	VERMP
Whole Vermis	VERMW
Fourth Ventricle	VENT4

“Proportional” volume measurements (expressed as percent)

Frontal Eye Fields to Brain Volume	FEFPPR = FEF/CAVOL x 100
Index	VERPPR = VERMP/VERMW x 100
Superior-Posterior to Whole Vermis	VENT4W = VENT4/VERMW x 100
Fourth Ventricle to Whole Vermis	

ADOLESCENT SCHIZOPHRENIA

Table 2: Patient symptom ratings

Global Assessment Scale	Brief Psychiatric Rating Scale	Positive and Negative Symptoms Scale			
$\bar{x}$ (SD)	$\bar{x}$ (SD)	<u>Subscales scores:</u>			
		Positive	Negative	General	Total
		$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)	$\bar{x}$ (SD)
48.33 (14.04)	40.42 (10.27)	15.08 (4.60)	20.00 (7.76)	34.58 (9.45)	69.67 (19.10)

ADOLESCENT SCHIZOPHRENIA

Table 3: Group comparisons of volumetric brain measurements

Absolute Volume Measurements (cm ³)				Proportional Volume Measurements (%)			
Index	Control $\bar{x}$ (SD)	Patient $\bar{x}$ (SD)	Results of Group Comparisons	Index	Control $\bar{x}$ (SD)	Patient $\bar{x}$ (SD)	Results of Group Comparisons
CAVOL	17.0(.97)	16.6(1.5)	$F=.44, p=.51$				
VENT4	.475(.19)	.493(.15)	$F=.06, p=.81$	VENT4W	14.71(6.23)	16.04(5.73)	$F=.27, p=.83$
VERMP	1.80(.44)	1.77(.24)	$F=.03, p=.86$	VERMPPR	54.46(9.51)	56.94(5.18)	$F=.58, p=.46$
VERMW	3.28(.26)	3.11(.31)	$F=1.95, p=.18$				
LFEF	4.41(.66)	3.89(.78)	$F=2.92, p=.10$				
RFEF	3.86(.71)	3.52(.80)	$F=1.13, p=.30$				
FEF	8.28(.90)	7.41(1.4)	$F=2.88, p=.11$	FEFPPR	48.89(6.15)	44.75(8.79)	$F=1.64, p=.21$

Note: $df=1, 21$

Table 4: Wisconsin Card Sorting Test (WCST) Performance ADOLESCENT SCHIZOPHRENIA

Index of Performance	Control $\bar{x}$ (SD; Range) $\bar{x}$ Rank	Patient $\bar{x}$ (SD; Range) $\bar{x}$ Rank	Results of Group Comparisons (df=12, 12)
Categories Achieved	6.0 (0.0; 6-6) 15	4.83 (1.95; 0-6) 10	$U=42.0, p=.015$
Perseverative Responses	8.92 (5.07; 5-24) 8.38	19.50 (11.10; 6-43) 16.63	$U=22.5, p=.004$
Perseverative Errors	7.17 (4.26; 5-20) 8.71	15.00 (8.95; 4-34) 16.29	$U=26.5, p=.008$
Non-Perseverative Errors	3.83 (3.64; 0-14) 8.04	15.25 (12.23; 3-40) 16.96	$U=18.5, p=.002$
Failure to Maintain Set	.083 (.29; 0-1) 8.83	1.0 (.85; 0-2) 16.17	$U=29.5, p=.003$
Sorting Efficiency (EFF)	.080 (0.011; .051-.088) 17.08	.050 (.026; .00-.086) 7.92	$U=19.5, p=.002$

ADOLESCENT SCHIZOPHRENIA

Table 5: Co-occurrence of impaired performance in the patient group

ID#	Impaired WCST	Abnormal Smooth Pursuit Tracking Rating		Fixation Suppression < 100%	MRI (rank within group)			
		Light	Dark		LFEF	RFEF	FEFPPR	VERMW
01		√	√		5	6	7	2
02	√	√	√		9	7	6	7
03	*	√	√	√	4	3	2	11
04					2	2	1	4
05	√	√		√	6	9	8	5
06	√	√	√	√	10	11	11	6
07	√				-	-	-	-
08	*	√	√		8	8	10	9
09					1	1	4	1
10		√			11	10	9	8
11	√			√	3	4	3	10
12	√	√	√		7	5	5	3

Notes.

"√" indicates a subject who has obtained what are considered to be 'abnormal' ratings on a task.

"*" indicates a subject whose score approached 'abnormal' levels.

For MRI data, a rank of "1" indicates the largest, and a rank of "11", the smallest volume.

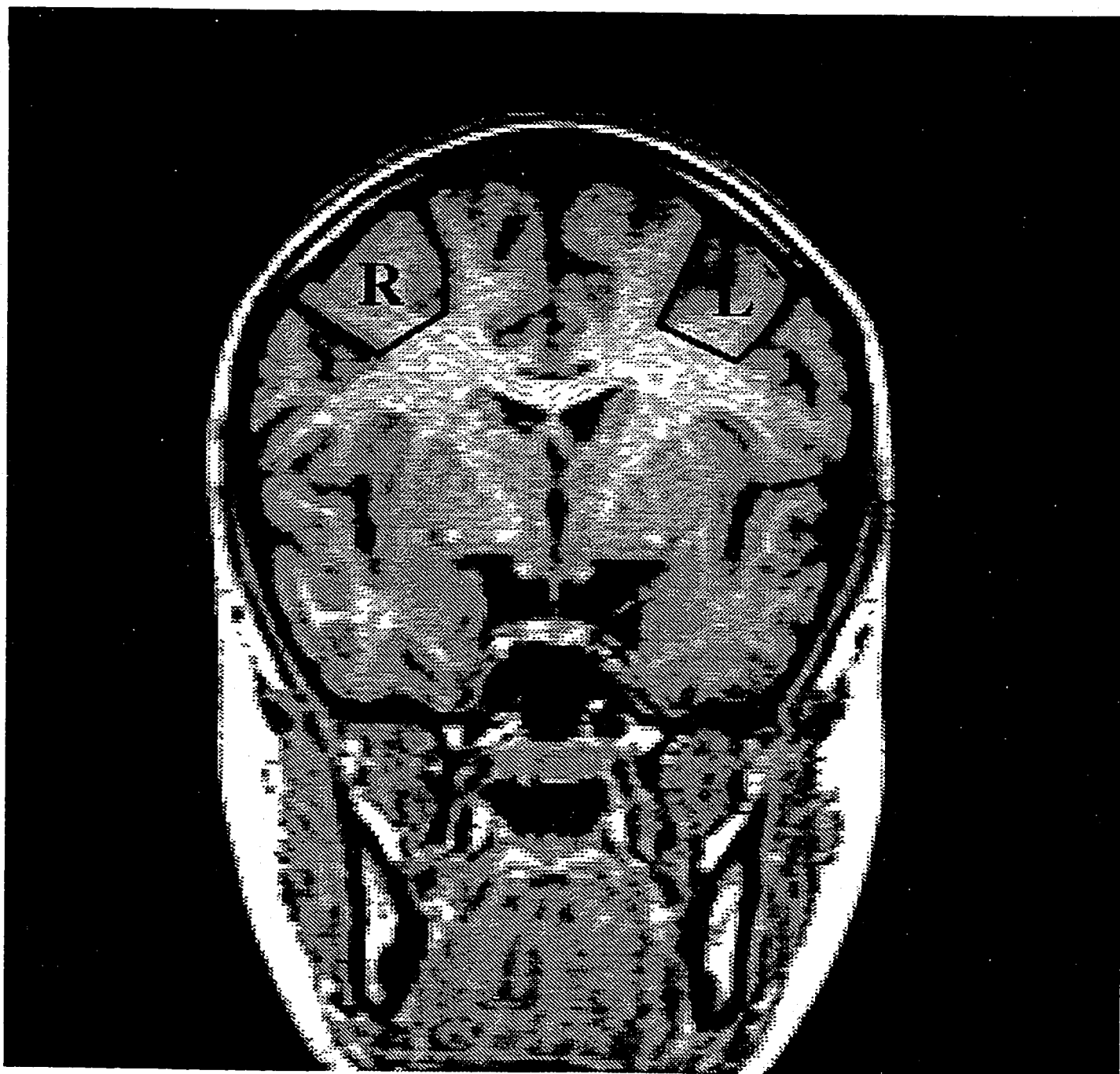


Figure 1. Coronal section with the right (1) and left (2) frontal eye fields outlined (left-right image reversal).

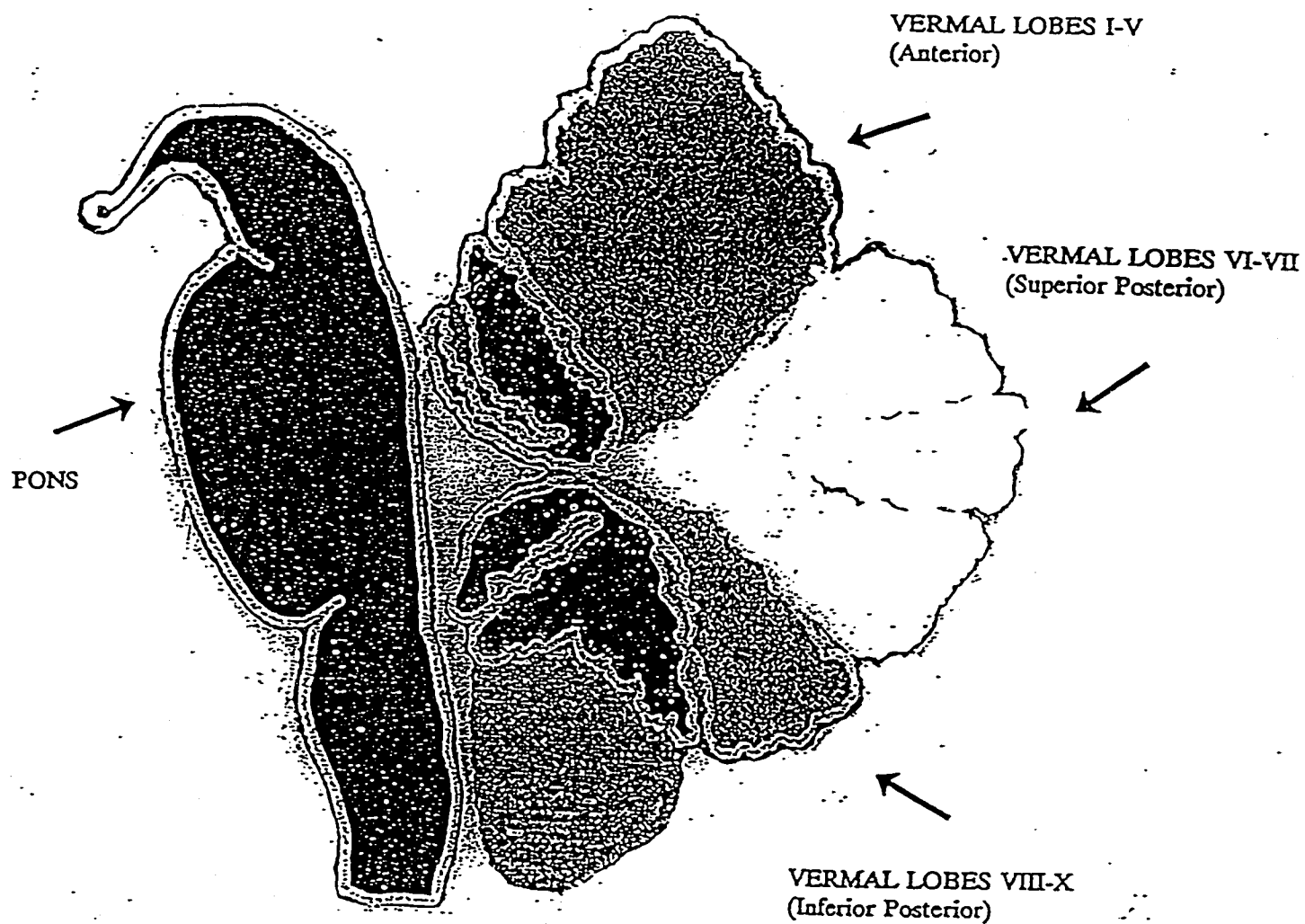


Figure 2. Schematic of the ventral pons and cerebellar vermis with detailed labelling indicating cerebellar structures, fourth ventricle, and pons.

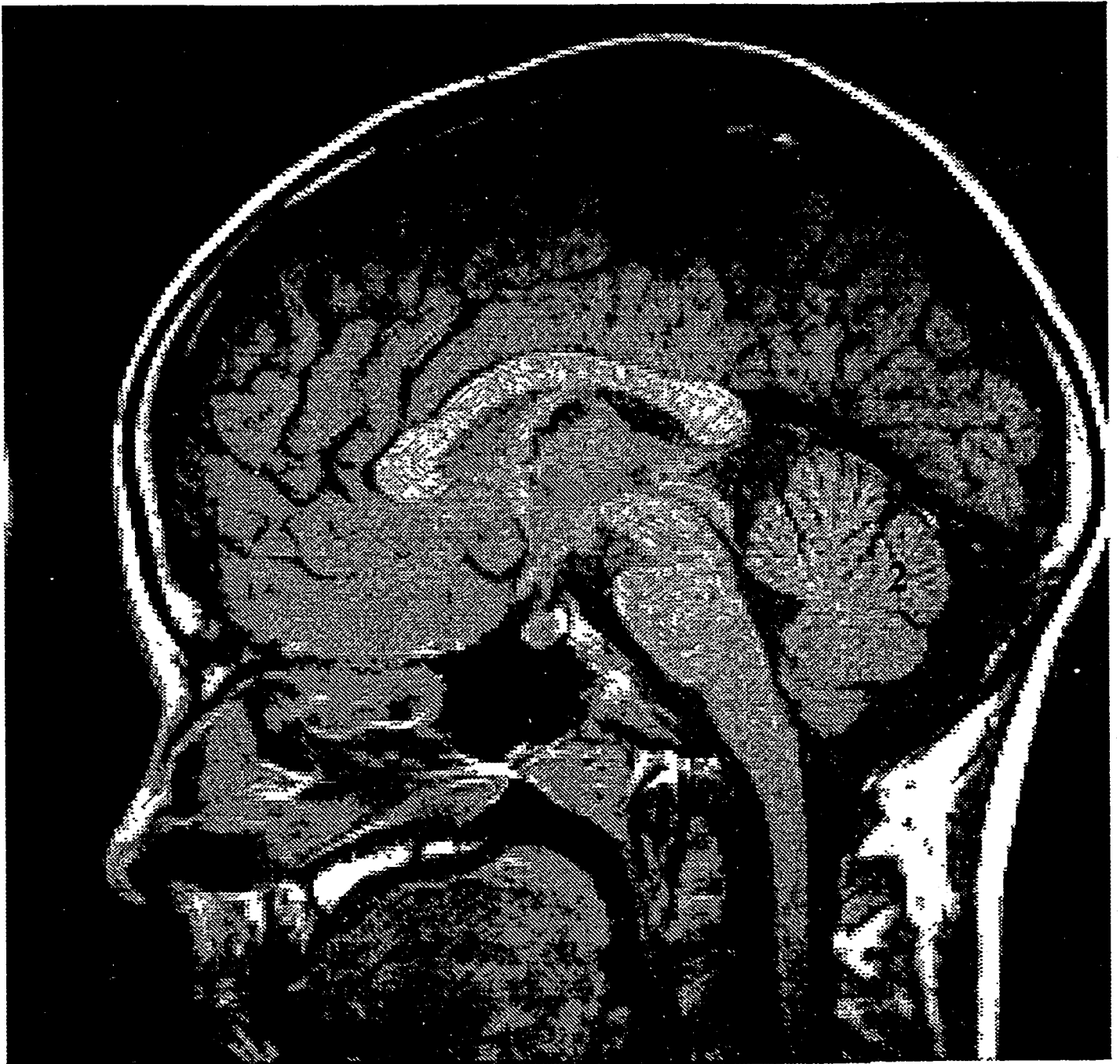


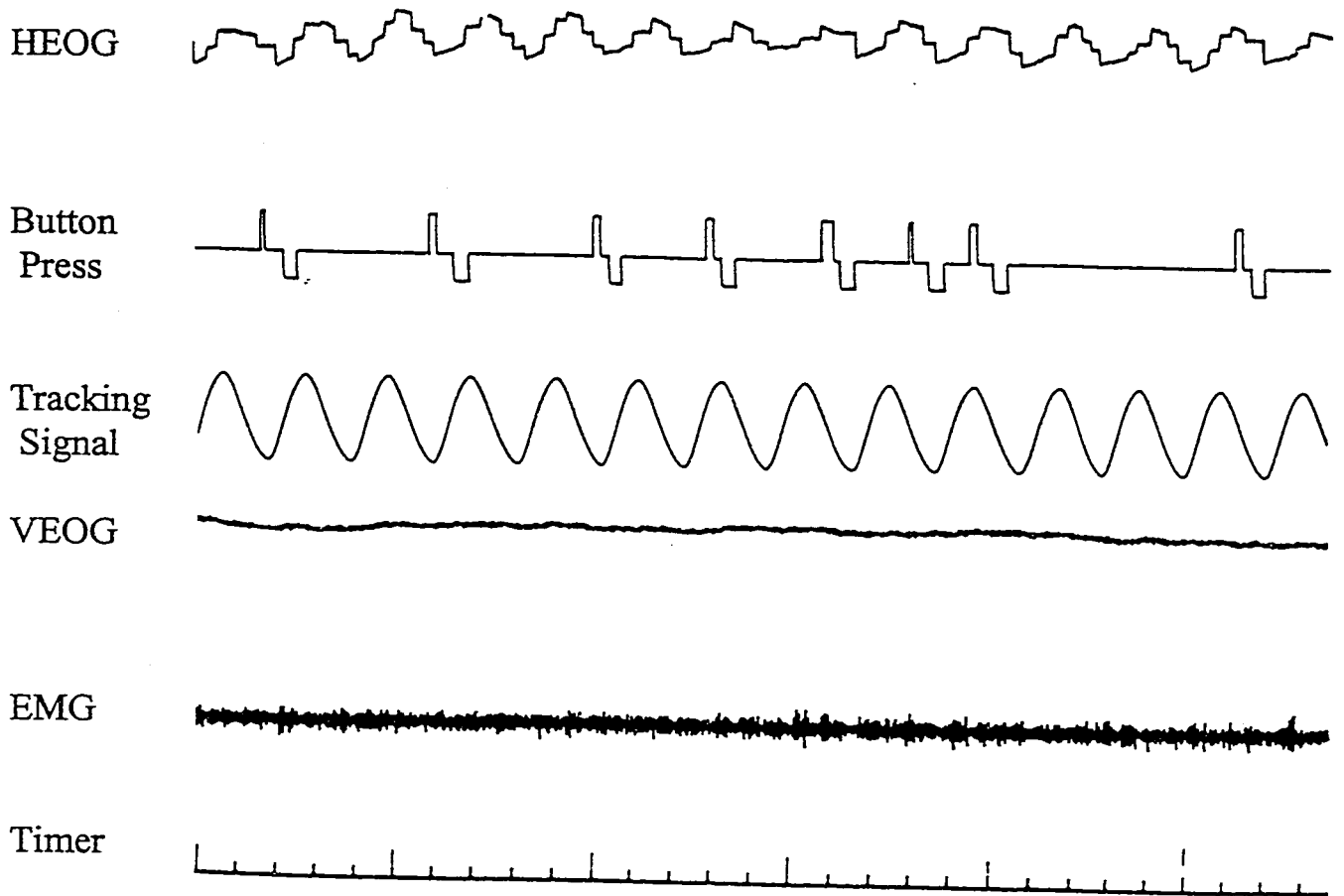
Figure 3. Midsagittal section with the fourth ventricle (1) and superior-posterior vermis (2) indicated



Figure 4. Variations in pursuit tracking measures as a function of group and condition.

Appendix A

Example of recording from 1 patient displaying poor tracking



Appendix B

Expanded Smooth Pursuit Tracking Rating Scale and Scoring Criteria

ADOLESCENT SCHIZOPHRENIA

(a)² 0 - Normal

1 - Questionable



(c) 2 - Abnormal



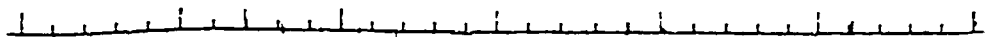
(d) 3 - Abnormal



4 - Abnormal



5 - Abnormal



Seconds

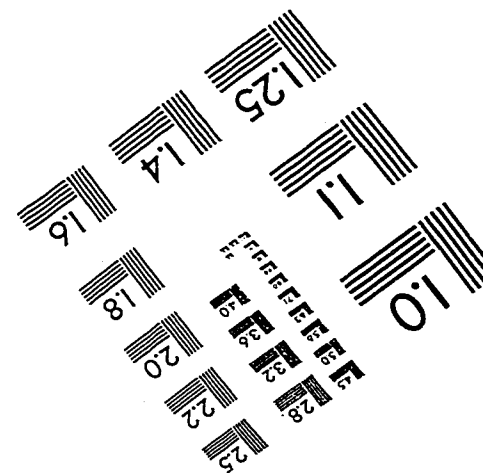
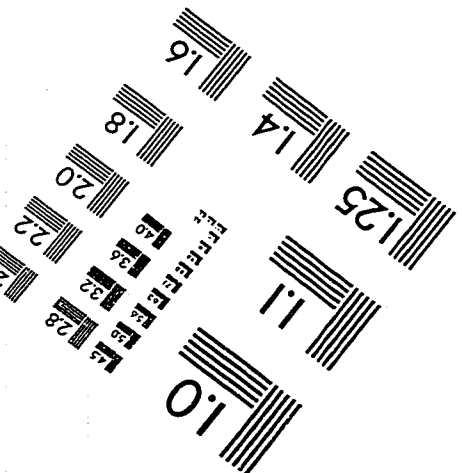
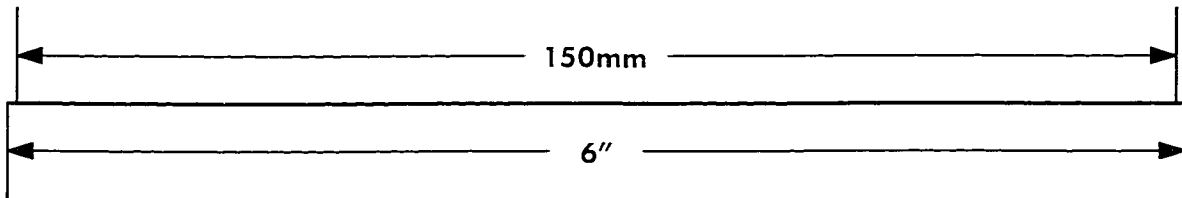
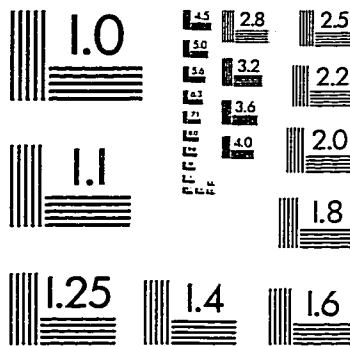
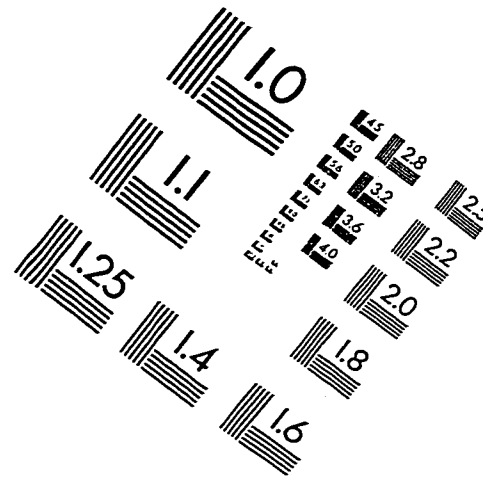
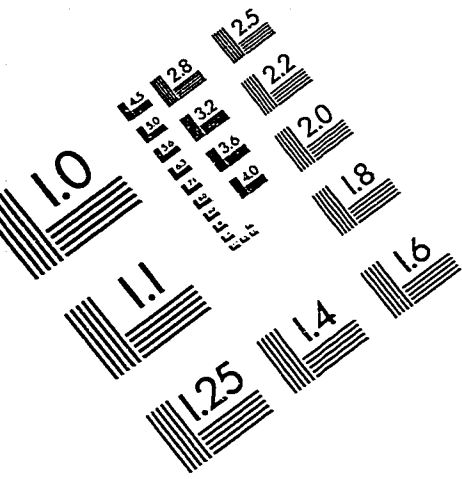
Note.⁴ Ratings according to Benitez (1974)

ADOLESCENT SCHIZOPHRENIA

Scoring Criteria

- | | |
|-------------------|--|
| 0 - Normal. | No indication of deviation. |
| 1 - Questionable. | Some indication of deviation, occurring on more than 1 and less than 7 out of 10 oscillations. |
| 2 - Abnormal. | Small deviations or squaring, occurring on 7 or more of 10 oscillations. |
| 3 - Abnormal | Large deviations or squaring clearly visible on 7 or more of 10 oscillations. |
| 4 - Abnormal. | Consistent pattern of deviations or squaring, apparent on every oscillation. |
| 5 - Abnormal | Consistent pattern of large deviations or squaring, apparent on every oscillation. |

IMAGE EVALUATION TEST TARGET (QA-3)



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1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989

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