Neuropsychological performance at the age of 13 years and adult schizophreniform disorder*

Prospective birth cohort study

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Summary We examined neuropsychological functioning at age 13 years in adolescents who later developed schizophreniform disorder, compared with healthy controls and with adolescents diagnosed as having had a manic episode or depression or anxiety disorder. Participants were from an unselected birth cohort. Attentional, executive and motor impairments at age 13 were found in those who later fulfilled diagnostic criteria for schizophreniform disorder, suggesting that these impairments may be the earliest emerging neuropsychological impairments in schizophrenia-related disorders.

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Despite hope of identifying a specific cognitive deficit characteristic of schizophrenia, generalised neuropsychological impairment is the most common finding in individuals with an established schizophrenic illness (Heinrichs & Zakzanis, 1998; Joyce & Huddy, 2004). Two key issues remain to be resolved. What are the earliest emerging neuropsychological impairments in schizophrenia? Are such impairments specific to schizophrenia-related disorders? We report data from a longitudinal birth cohort study on neuropsychological functioning at the age of 13 years in relation to adult psychiatric outcomes at 26 years.

METHOD

Participants were members of the Dunedin Multidisciplinary Health and Development Study – a prospective general-population birth cohort of 1037 individuals born in Dunedin, New Zealand, between April 1972 and March 1973. Study members were assessed on ten occasions between the ages of 3 and 26 years (Poulton *et al*, 2000; Cannon *et al*, 2002). The protocol was approved by the ethics review boards of the three participating universities.

Psychiatric interviews using the Diagnostic Interview Schedule (Robins *et al*, 1995) were available at the age of 26 years for 979 of the 1019 cohort members still living (96%). Research diagnoses of past-year Axis 1 disorders were grouped for this analysis into the following: schizophreniform disorder (3.7%), manic episode (2.0%) and depressive or anxiety disorder (28.5%). The remainder of the Dunedin Study members comprised the control group. Because the youth of the cohort made the ultimate diagnostic outcome uncertain for some, we grouped study members meeting criteria for schizophrenia (1% of the cohort) and schizophreniform disorder (2.7% of the cohort) under the term schizophreniform disorder. Diagnostic procedures are described elsewhere (Poulton *et al*, 2000; Cannon *et al*, 2002). Briefly, data from interviews and collateral reports were used to make research diagnoses. All those receiving this diagnosis reported both hallucinations and delusions, and 70% had received treatment. Interviewers were masked to previous neuropsychological data.

In 1985–1986, two clinical psychologists administered a 50-min neuropsychological test battery to the Dunedin Study Members. The battery comprised: Rey–Osterreith Complex Figure Test; Rey Auditory–Verbal Learning Test (four trials); Wisconsin Card Sort Test (three categories); Mazes; Trail Making Test; Grooved Pegboard and Verbal Fluency (Lezak, 1983). Only Dunedin Study members with both diagnostic data at the age of 26 years and neuropsychological data at the age of 13 years (69% of the cohort) could be included in this analysis. Participants who were missing either did not take part in the assessment at 26 years of age (4%) or the assessment at 13 years of age (14%), lived too far away to come to the unit for neuropsychological testing (11%), or were unable to undergo testing for varied reasons (2%). The children who underwent testing did not differ significantly from the remainder of the cohort on measures of family socio-economic status, IQ, gender, or behaviour problems (Frost *et al*, 1989). A similar proportion of the children who were tested developed an adult schizophreniform disorder outcome, as compared with the whole cohort (3.5% *v.* 3.7%).

To examine specific cognitive functions within the context of broadly normal IQ, we excluded Dunedin Study members with IQ scores of >2 s.d. below the mean (n=16). One participant who had suffered a severe head injury was also excluded. Ultimately, 699 individuals were included in this analysis, comprising four groups: schizophreniform disorder (n=23); mania (n=10); depression/anxiety disorder (n=196); and controls (n=470). Test scores were standardised so that mean=0 and s.d.=1. Regression equations were performed using three dummy variables (one for each diagnostic status) and using the control group as the reference category. All regression coefficients were adjusted for gender and average socio-economic status of the family throughout childhood and adolescence (Wright *et al*, 1999).

RESULTS

At age 13, the schizophreniform disorder group differed significantly from the control group on the following test scores: Trail Making Test, part B score, time to completion: β=−0.76, 95% CI −0.35 to −1.2, P<0.001; Trail Making Test, part B score minus part A score: β=−0.74, 95% CI −0.33 to −1.16, P<0.001; Grooved Pegboard, right hand: β=−0.68, 95% CI −0.22 to −1.1, P=0.002; Grooved Pegboard, left hand: β=−0.41, 95% CI −0.008 to −0.81, P=0.045 (Pegboard effects persisted following adjustment for hand preference); and Verbal Fluency: β=−0.46, 95% CI −0.91 to −0.02, P=0.043. All significant differences between schizophreniform *v.* control groups were in the moderate range, s.d.=0.4–0.8. The mania group did not differ significantly from the control group on any test score at age 13 years. Although this study had poor power to detect differences between mania *v.* control groups, Fig. 1

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shows that the effects were generally not as large as the differences between schizophreniform *v.* control groups, and for some tests (i.e. Trail-Making Test and Grooved Pegboard) differences were in the opposite direction. The depression and anxiety group differed significantly from the control group only on the Trail Making Test, part A (β=−0.23, 95% CI −0.06 to −0.4, *P*=0.008) and part B (β=−0.19, 95% CI −0.03 to −0.36, *P*=0.02). Effect sizes for the differences between depression and anxiety group and control group were not as large as the differences between the schizophreniform group and control group (Fig. 1). The study had ample power to detect the small differences between the depression and anxiety group and control group.

DISCUSSION

This study is limited by the small number of Dunedin Study members having schizophrenia-related disorders or mania, and by the rather old-fashioned nature of the neuropsychological battery. However, these limitations are compensated for by the prospective nature of the data. Our results expand on previous work showing that impairments in motor performance and attentional or executive performance are evident many years before onset of schizophrenia (Erlenmeyer-Kimling *et al*, 2000; Niendam *et al*, 2003), and suggest the hypothesis that integrated higher-level cortical activity is already affected. Our findings correspond to the speed-of-processing dimension identified as one of seven separable cognitive factors in schizophrenia (Neuchterlein *et al*, 2004).

There are two noteworthy aspects to our results. First, memory and learning impairments were not found in the current analysis but are evident in studies of first-episode patients, indicating that these impairments may emerge later in the developmental course of the disorder (e.g. Joyce *et al*, 2002). Second, our results suggest some specificity of early motor and attentional or executive impairment to future schizophrenia-related outcomes rather than affective disorder outcomes (though power was limited by the size of the mania group).

This study further emphasises the importance of studying cognitive impairment in schizophrenia within the context of brain development (Thompson *et al*, 2001).

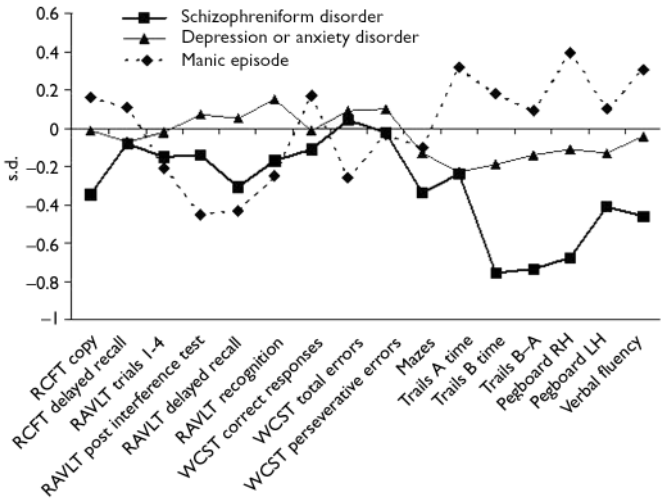

Fig. 1 Standardised scores on a neuropsychological test battery for 13-year-olds who later developed schizophreniform disorder (*n*=23), manic episode (*n*=10) or depression or anxiety disorder (*n*=196). The regression coefficients are interpretable as s.d. unit differences between each psychiatric group and the control group, adjusted for gender and family socio-economic status. RH, right hand; LH, left hand; RCFT, Rey–Osterreith Complex Figure Test; RVLT, Rey Auditory–Verbal Learning Test; WCST, Wisconsin Card Sort Test.

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REFERENCES

Cannon, M., Caspi, A., Moffitt, T. E., *et al* (2002) Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder. *Archives of General Psychiatry*, **59**, 449–456.

Erlenmeyer-Kimling, L., Rock, D., Roberts, S. A., *et al* (2000) Attention, memory and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High Risk Project. *American Journal of Psychiatry*, **157**, 1416–1422.

Frost, L. A., Moffitt, T. E. & McGee, R. (1989) Neuropsychological correlates of psychopathology in an unselected cohort of young adolescents. *Journal of Abnormal Psychology*, **98**, 307–313.

Heinrichs, R. W. & Zakzanis, K. K. (1998) Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*, **12**, 426–445.

Joyce, E. & Huddy, V. Y. V. (2004) Defining the cognitive impairment in schizophrenia. *Psychological Medicine*, **34**, 1151–1155.

Joyce, E., Hutton, S., Mutsatsa, S., *et al* (2002) Executive dysfunction in first episode schizophrenia and relationship to duration of untreated psychosis. *British Journal of Psychiatry*, **181** (suppl. 43), s38–s44.

Lezak, M. D. (1983) *Neuropsychological Assessment*, 2nd edn. New York: Oxford University Press.

Neuchterlein, K. H., Barch, D. M., Gold, J. M., *et al* (2004) Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, **72**, 29–39.

Niendam, T., Bearden, C. E., Rosso, I. M., *et al* (2003) A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *American Journal of Psychiatry*, **160**, 2060–2062.

Poulton, R., Caspi, A., Moffitt, T. E., *et al* (2000) Children's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Archives of General Psychiatry*, **57**, 1053–1058.

Robins, L. N., Cottler, L., Bucholz, K., *et al* (1995) *The Diagnostic Interview Schedule for DSM–IV*. St Louis, MO: Washington University School of Medicine.

Thompson, P. M., Vidal, C., Giedd, J. N., *et al* (2001) Mapping adolescent brain change reveals dynamic wave of accelerated gray matter loss in very early-onset schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, **98**, 11650–11655.

Wright, B. R. E., Caspi, A., Moffitt, T. E., *et al* (1999) Reconsidering the relationship between SES and delinquency: causation but not correlation. *Criminology*, **37**, 175–194.