Executive (frontal) dysfunction and negative symptoms in schizophrenia: apparent gender differences in 'static' *v.* 'progressive' profiles

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Background While executive (frontal lobe) dysfunction appears to be a core feature of schizophrenia, its relationship to psychopathology, age and duration of illness has yet to be explored systematically between the genders.

Method Executive dysfunction, positive and negative symptoms were evaluated in 27 male and 21 female in-patients who were unusually well-matched on numerous demographic and clinical measures.

Results Measures of executive dyscontrol and negative symptoms were highly associated in both genders. However, while both executive dyscontrol and negative symptoms increased prominently with age/duration of illness among women, no such relationship was evident among men.

Conclusions The similarly prominent levels of current executive dyscontrol and negative symptoms in male and female patients appear to have emerged via processes that differ fundamentally between the genders; among males these deficits appear to emerge and become 'locked in' earlier in the course of illness and to show little subsequent increase, while among females these same deficits appear to be less evident early in the course but to increase in prominence thereafter.

It is widely recognised that patients with schizophrenia show impairment of cognitive function; indeed, the essential universality of this finding indicates cognitive dysfunction to be one of the fundamental characteristics of the illness, though the nature of this impairment continues to be the subject of considerable uncertainty at several levels (Frith, 1995; Goldberg & Gold, 1995).

Firstly, is such impairment over-represented in, or even specific to, particular aspects of neuropsychological functioning? For example, executive functions, which orchestrate simple ideas, movements or actions into complex, goal-directed behaviour through the use rather than the processing of information, are associated traditionally with integrity of the frontal lobes and are widely recognised to be impaired in schizophrenia; however, the extent to which this impairment might constitute a primary feature of the illness or one element among much more widespread deficits is less clear (Saykin *et al*, 1991; Blanchard & Neale, 1994; Morice & Delahunty, 1996).

Secondly, what is the relationship of cognitive dysfunction to domains of psychopathology? For example, the extent of executive (frontal) deficit has been associated with the severity of negative symptoms in some studies, suggesting a common or overlapping pathophysiology (Breier *et al*, 1991; Hammer *et al*, 1995); however, this has not been found in all studies (Liddle & Morris, 1991; Chen *et al*, 1996*a*).

Thirdly, what is the course of cognitive impairment over the lifetime trajectory of the illness? While neuropsychological deficits are already evident at the first psychotic episode (Bilder *et al*, 1992; Hoff *et al*, 1992; Saykin *et al*, 1994), there endures a debate over whether these remain stable thereafter in the manner of a 'static encephalopathy' (Goldberg *et al*, 1993; Heaton *et al*, 1994) or continue to increase, in the manner of a deteriorating illness (Bilder *et al*, 1992; Davidson *et al*, 1995). This issue is of fundamental importance to how schizophrenia is conceptualised *vis-à-vis* neurodevelopmental and progressive arguments, and to whether these represent antithetical or complementary perspectives of the disorder (Waddington, 1993*a*; Weinberger, 1987, 1995; Waddington *et al*, 1997).

The 'levels of understanding' model argues that schizophrenia can be understood only through clarification of how its abnormalities at different levels interact with one another, with neuropsychology as the (putative) intermediary between psychopathology and neuropathology (Mortimer & McKenna, 1994). In this context, there endures considerable interest in the deficits of many older, chronically ill in-patients who manifest marked cognitive dysfunction and prominent negative symptoms (Buhrich *et al*, 1988; Arnold *et al*, 1995; Davidson *et al*, 1995); however, the severity of their overall cognitive impairment usually renders them inaccessible using classical tests of frontal lobe function such as the Wisconsin Card Sorting Test (WCST). It is now possible to access frontal lobe function on a background of such marked, generalised cognitive impairment using the Executive Interview (EXIT; Royall *et al*, 1992, 1993); thus we have explored the interrelationships of executive dyscontrol, more generalised cognitive dysfunction, psychopathology and age/chronicity of illness among an unusually homogeneous population that extends from patients in their 30s and 40s through to the very elderly. Given the evidence for gender differences in several aspects of the course of schizophrenia (Lewis, 1992; Waddington, 1993*a*), from developmental origin to neuropsychological impairment (Goldstein *et al*, 1994), a particular emphasis was placed on evaluating these parameters separately in male and female patients.

METHOD

Subjects

The subjects were 52 patients who constitute the survivors of a naturalistic population of initially 101 patients in the seven long-term wards of St Davnet's Hospital, Monaghan; all satisfied the Washington University criteria of Feighner *et al* (1972) for a diagnosis of schizophrenia. They represented the complement of patients with this diagnosis who had required admission to long-term care from Cavan–Monaghan, a region of rural Ireland evidencing substantial ethnic, socioeconomic and nosocomial homogeneity; the region had

https://doi.org/10.1192/bjp.171.2.154 Published online by Cambridge University Press

been serviced by a single psychiatric hospital, St Davnet's, through which essentially all care had been provided. This cohort, the 'Monaghan 101', was first studied in 1983, as described previously in detail (Waddington *et al*, 1987), and has been re-assessed longitudinally after five years (Waddington *et al*, 1990) and 10 years (Waddington *et al*, 1995; Waddington & Youssef, 1996). Over this 10-year period there was little overall progression to a state of gross defect, as defined qualitatively, but psychopathological and neuropsychological assessments were too limited both in scope and in sensitivity to allow us to address the present issues. The present study constitutes a 12-year follow-up undertaken in 1995 using entirely different procedures; it includes newly introduced, more sensitive assessment instruments which were not available during earlier phases of this longitudinal study. Increasing natural mortality (49 of the 101 patients died between 1983 and 1995) vitiates further long-term follow-up, hence only cross-sectional data are available. Current antipsychotic dosage, as chlorpromazine (CPZ) equivalents (Davis, 1976), and exposure to anticholinergics were recorded.

Assessment of psychopathology

Each patient's current psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987); positive and negative symptom subscale scores (Kay, 1991) were determined.

Assessment of cognitive function

Each patient's general cognitive function was assessed using the Mini-Mental State Examination (MMSE; Folstein *et al*, 1975). Executive (frontal) cognitive function was assessed using the EXIT; this 25-item instrument, which defines in increasing scores (0–50; 'normal' range: young adults $\leqslant 5$, elderly adults $\leqslant 10$) the behavioural sequelae of executive dyscontrol (particularly imitation behaviour, perseveration, frontal release signs and utilisation behaviour), has been shown previously to manifest high internal consistency and interrater reliability when applied to patients whose deficits are so prominent as to preclude the use of instruments such as the WCST (Royall *et al*, 1992, 1993).

Data analysis

Data are expressed as means (s.d.) or prevalences (%) and were analysed using Student's *t*-test, chi-squared test or Pearson product moment correlation (two-tailed).

RESULTS

Data on each of the study variables were available for 48 of the 52 patients (27 men, age range 36–89; 21 women, age range 42–88) and it is to this group that all further discussion relates. These patients were characterised typically by onset of illness (defined by first hospital admission) in the mid-20s, more than four decades of continuous illness and being now in their late sixties, and manifested currently comparatively few positive symptoms (low PANSS-positive scores) but a predominance of negative symptoms (high PANSS-negative scores), general cognitive impairment (low MMSE scores) and executive dyscontrol (high EXIT scores); none of these characteristics (Table 1) differed significantly between male and female patients. Patients were currently receiving doses of antipsychotics that did not differ between men and women (741 (s.d. 1108) *v.* 1040 (s.d. 1180) mg CPZ equivalents, respectively); similarly, there was no significant gender difference in the extent of current exposure to anticholinergics (14 of 27 men (52%) *v.* 13 of 21 women (62%)).

In both male and female patients, PANSS-negative symptom, MMSE and EXIT scores were strongly correlated measures (Table 2); PANSS-positive symptom score was uncorrelated with PANSS-negative symptom, MMSE or EXIT scores among patients of either gender (*r* values in the range 0.01–0.15, NS). However, while general cognitive impairment on the MMSE increased prominently with age in both men and women, PANSS-negative score and EXIT dysfunction each increased with age only in women (Table 2). For each gender, age and duration of illness were very highly correlated (males: $r=0.87$, $P<0.001$; females: $r=0.67$, $P<0.001$); thus, very similar results were found on substituting duration of illness for age in these analyses.

There were no significant relationships between either current dosage of antipsychotics or current exposure to anticholinergics and PANSS-negative symptom, MMSE or EXIT scores, other than a marginal association ($r=0.41$, $P<0.05$) between current dose of antipsychotics and higher MMSE score among males; while a trend in the same direction among females did not itself attain significance ($r=0.17$, NS), these two correlations did not differ significantly ($P>0.4$) from one another.

Table 1 Demographics of patients (means (s.d.))

	Male	Female
Number	27	21
Age	69.4(12.7)	66.2(12.7)
Age at onset	24.7(6.3)	25.1(9.5)
Duration of illness	44.6(11.2)	41.1(9.0)
PANSS-positive	12.2(3.5)	11.9(2.7)
PANSS-negative	32.1(9.4)	32.1(7.8)
MMSE	12.4(6.7)	14.9(7.8)

DISCUSSION

This study concerns two groups of male and female patients who could not be distinguished demographically in terms of age, age at onset and duration of illness, or clinically in terms of either positive or negative psychopathology, general or executive cognitive dysfunction. Though the onset of psychosis in schizophrenia is held traditionally to occur later in women than in men (Lewis, 1992; Faraone *et al*, 1994), several recent studies have failed to note such an

Table 2 Correlation matrix for male and female patients

	MMSE	EXIT	PANSS-negative
Males			
Age	−0.60***	0.13†	0.21†
MMSE		−0.63***	−0.65***
EXIT			0.73***
Females			
Age	−0.58**	0.64**	0.72***
MMSE		−0.87***	−0.75***
EXIT			0.76***

** $P<0.01$; *** $P<0.001$.
† $P<0.05$ *v.* females.

https://doi.org/10.1192/bjp.171.2.154 Published online by Cambridge University Press

effect (Beiser *et al*, 1993; Andia *et al*, 1995), including the most recent study in rural Ireland (Kendler & Walsh, 1995). Similarly, though clinical phenomenology and outcome in schizophrenia are held traditionally to be more benign in women than in men (Goldstein & Link, 1988; Lewis, 1992), some recent studies have failed to note such effects (Perlick *et al*, 1992; Andia *et al*, 1995; Goldberg *et al*, 1995), including again the most recent study in rural Ireland (Kendler & Walsh, 1995). It should be noted that the present population is one of chronically ill in-patients that self-selects for both males and females with more severe impairment. When the above are considered together with substantial ethnic, socioeconomic and nosocomial uniformity, these male and female patients evidence unusual and striking homogeneity across several dimensions and thus present a rare opportunity to compare the genders in very closely matched samples.

There has been considerable debate over whether negative symptoms and cognitive impairment share a common pathophysiology, with any relationship between such symptoms, executive dyscontrol and frontal lobe dysfunction receiving particular scrutiny (Frith, 1995; Goldberg & Gold, 1995). Among the present patients, negative symptoms (i.e. psychomotor poverty) but not positive (i.e. reality distortion and disorganisation), general cognitive impairment and executive dyscontrol constituted a nexus of highly intercorrelated variables; a putative role in this for frontal dysfunction is also suggested by recent studies which have associated both negative symptoms (Merriam *et al*, 1990) and executive dyscontrol (Cuesta *et al*, 1996) with neurological signs attributable to such dysfunction. To our knowledge, this nexus has not been compared systematically among well-matched groups of male and female patients and at this level we find that it does not differ psychometrically between the genders.

In considering how general cognitive impairment, executive dyscontrol and negative symptoms might vary with age and duration of illness, it must be emphasised that age and duration of illness were themselves very highly intercorrelated variables, in both men and women, as would be expected among such older in-patients for a disorder of typically early onset and chronic course. In the present population, therefore, these variables constitute an unresolvable confound and so we refer henceforth to age/duration of illness. General cognitive impairment, which was marked in this population, increased prominently with age/duration of illness, in agreement with recent reports using the MMSE in demographically similar patients (Arnold *et al*, 1995; Davidson *et al*, 1995); we find this effect to be indistinguishable between men and women. However, the fundamental finding of the present study concerns executive dyscontrol and negative symptoms, both of which were also marked in this population; these deficits increased prominently with age/duration of illness among women while no such relationship was evident among men. Although there has not been any previous systematic comparison between the genders, it is notable that three recent studies reporting that evident neuropsychological (including executive) dysfunction and negative symptoms did *not* deteriorate further with age/duration of illness involved primarily or exclusively male patients (Goldstein *et al*, 1991; Ring *et al*, 1991; Chen *et al*, 1996*b*). Furthermore, within each gender in the present study the profiles of executive dyscontrol and negative symptoms are highly similar, suggesting a pathophysiological intimacy (perhaps fronto-striatopallidothalamic; see Waddington, 1993*b*; Elliott *et al*, 1995). Also, it would appear that the domains accessed by elements of the MMSE show greater psychometric overlap in women than in men with those domains co-accessed by the EXIT and PANSS-negative symptom subscale.

Before trying to make longitudinal interpretations of cross-sectional data, we must consider possible biases that might differentially influence selection of men *v.* women for long-term hospital care. Such biases are difficult to exclude incontrovertibly; for example, might negative symptoms be a less serious obstacle to community living in younger women but a more serious obstacle in their later life? For men, might other factors such as socially objectionable behaviour play a larger role in the need for hospital care across the whole age span? However, any such bias would be reflected in a generally older age at admission for women, whereas no such effect was evident; furthermore, female patients were, if anything, the more likely to have a history of recurrent disruptive and aggressive behaviour. The overall comparability of the present male and female patients in multiple demographic terms (Table 1) is striking, and it has been argued cogently that any contribution from such potential sampling biases to studies of gender differences in schizophrenia is limited (Goldstein, 1993).

Thus, our principal finding is that the very similar, prominent levels of current executive dyscontrol and negative symptoms in the present samples of male and female patients appear to have occurred via processes that may differ between the genders: among men, prominent executive dyscontrol and negative symptoms would each appear to deteriorate and become 'locked in' as a more 'static' deficit relatively early in the course of the illness and to increase only little thereafter, even over decades; conversely, among women these same features would each appear to be less evident earlier in the course of illness but to deteriorate as a more 'progressive' deficit over those same decades of illness. This would be consistent, at least in part, with a model in which the neurodevelopmental basis of schizophrenia (Waddington & Buckley, 1996) is somewhat more prominent among males, while females show a somewhat different course (Lewis, 1992; Waddington, 1993*a*; Castle *et al*, 1993; Goldstein *et al*, 1994). However, it must be emphasised that the capacity of cross-sectional studies to sustain such longitudinal interpretations is not clear unless confirmed prospectively; and the extent to which findings in our patients might generalise to other populations, whose severity and duration of illness might be different, remains to be determined. Furthermore, there is the challenge of specifying the extent to which the present findings might be occurring over any particular phase(s) of the lifetime course of schizophrenia (Waddington *et al*, 1997), from childhood psychosocial antecedents, through the initial period of psychosis (Scully *et al*, 1996) to enduring chronic illness, as an additional clue to the process(es) involved and how they differ between the genders.

ACKNOWLEDGEMENT

We are grateful to the Stanley Foundation for their support.

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https://doi.org/10.1192/bjp.171.2.154 Published online by Cambridge University Press

CLINICAL IMPLICATIONS

- Executive dysfunction and negative symptoms are intimately associated in schizophrenia.
- These deficits increase with age/duration of illness in females but are of static prominence in males.
- Comparable current deficits in males and females appear to evolve via distinct illness trajectories.

LIMITATIONS

- Longitudinal conclusions derived from cross-sectional data.
- Possible sampling bias between the genders.
- Generalisability in other patient populations.

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(First received 27 August 1996, final revision 27 January 1997, accepted 7 February 1997)

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https://doi.org/10.1192/bjp.171.2.154 Published online by Cambridge University Press

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